THE AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY

VOL. 43 JUNE, 1940 No. 6

CLINICAL CONSIDERATION OF THE STOMACH*

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CLINICAL consideration of the stomach is such a broad subject that it is obvious that I can only briefly discuss a few of its clinical aspects.

One condition which I feel merits much more consideration than it has received in the past is the symptom complex called pylorospasm. Pylorospasm might be defined as a spastic contraction of the thickened circular stomach muscle coat known as the pyloric sphincter, which at times produces various gastric disturbances.

Even though the definition seems fairly simple our knowledge of the causes of this condition is very limited. The reasons for this are more or less obvious. In the first place, the stomach of the intact human subject is quite inaccessible and studies under normal and abnormal conditions are chiefly by indirect methods. In general the methods of study are limited to: (1) the correlation of clinical symptoms with the pathological findings so well brought out in about 1830 by Cruveilhier; (2) by direct observation during surgical operations; (3) direct observation of the pylorus through gastrostomy openings such as done by Beaumont over one hundred years ago and recently by Carlson; (4) visualization of the stomach by means of the roentgen ray, following various procedures such as the giving of certain foods and drugs and noting their effects; (5) gastroscopic examination.

Other reasons for our lack of knowledge of this subject are that the physiological control of the pylorus is very complex and its response to stimulation is dependent upon the state of the organ at the time it is stimulated. The results obtained experimentally depend upon such conditions as the strength and frequency of the stimulus and the level of the tone of muscle at the time. The sympathetic component of the vegetative nervous system is generally considered to be inhibitory to the pyloric sphincter and the vagus motor in its action, but an opposite effect may be obtained from either nerve, the tonus at the time appearing to be a determining factor.

Thus it is quite evident that this variability of response seems to be characteristic of gastric nerves and this in turn may help us better to understand the so-called paradoxical effects we get with certain drugs at times. Also, a better knowledge of the chemical as well as nervous control of physiological function and the manner in which it may be altered both physically and psychically may lead us far forward

* Read at the Fortieth Annual Meeting, American Roentgen Ray Society, Chicago, Ill., Sept. 19–22, 1939.

in the understanding of the variability of symptoms. This is certainly the rule in clinical medicine.

The etiologic factors in pylorospasm may be (a) intrinsic or (b) extrinsic.

(a) Under the intrinsic causes the most common is a peptic ulcer of the stomach or duodenum.

(b) Under extrinsic causes we have:

Reflex factors due to *organic lesions* outside of the stomach, such as the presence of gallstones, which in themselves may be producing no localizing symptoms at times but only this so-called indigestion picture. It is often stated that gallstones may remain for a period of years in the gallbladder without producing any symptoms. If we will amplify this statement by adding the phrase "symptoms referable to gallbladder" we will then be much more accurate, because if a careful history is taken it well be found that often such patients have had attacks of so-called acid stomach or indigestion. Waiting for severe pains in these cases before removing the stones does not seem to be warranted. Pylorospasm may be produced by a slight change in position of the stones.

Appendicitis is another important cause of pylorospasm. Renal calculi, pyelitis, and diseases of the genitalia are others.

Reflex symptoms due to functional disturbances in other organs may occur as in the so-called irritable colon. Smith and his coworkers feel that the localized epigastric distress commonly associated with this irritability of the colon is gastric in origin and is brought about by reflex stimulation of the stomach.

Such findings agree with the observations of Carlson on animals that sufficient stimulation of all sensory visceral nerves may produce a contraction of the pylorus. Clinically, one wonders if these are not both local expressions of a constitutional defect, and that the particular organ or structure having the lowest threshold is the one which produces symptoms. Biliary dyskinesia may be another symptom complex explained in the same manner.

Under *systemic causes* of pylorospasm one can include:

(1) Allergic states brought about by the ingestion of some of the more common offenders, as milk, eggs and shell fish, to which the particular individual is sensitive. The same findings as in bronchial asthma occur, namely, spasm of smooth muscle and edema of the mucous membrane.

(2) Toxic states caused by the excessive use of tobacco.

(3) Endocrine disturbances. Symptoms of dysfunction as manifested at the time of menstruation and the menopause are commonplace. The signs and symptoms associated with the neuromuscular imbalance in both hyperthyroid and hypothyroid states often are encountered.

Diseases of the central nervous system such as tabes dorsalis may be an occasional cause. Gastric crises examined roentgenologically during an attack may show nothing but a pylorospasm.

An organic lesion of the brain such as a tumor may be another productive agent.

Psychoneurosis as a cause of pylorospasm possibly occurs with much greater frequency than is at present suspected.

If the spasm is of short duration in any one of these conditions there may be no dilatation of the stomach, but if persistent and prolonged, a dilatation may occur due to the associated hyperperistalsis and hypersecretion.

It is obvious from the foregoing that, clinically viewed, our methods of study for the diagnosis of pylorospasm are limited to a very few procedures.

It can be seen, therefore, that there must be close cooperation between the clinician and the roentgenologist.

A careful history and its proper interpretation are of great importance because there may be nothing abnormal on physical examination even in the presence of either a functional or an organic disturbance of the gastrointestinal tract.

Further, one must have some understanding of the mode of production of the patient's subjective complaints and the

way in which they may be modified by his environment.

There are facts brought out in the history which in some cases may be of great importance to the roentgenologist in his recognition of early pathology. In turn, the diagnosis of the clinician is verified or disproved. If organic changes are present the exact position of the pathological lesion is brought out, and if surgical measures are indicated they can be carried out at an early date, allowing a distinct advantage in prognosis. The clinician is also able to follow the results of his therapy by routine examination in selected cases.

Another condition which I desire to bring to your attention is the seasonal incidence of the symptomatology in peptic ulcer. Moynihan many years ago emphasized it and stressed the constitutional type of individual in which it occurred.

Einhorn also stressed it and brought out the fact that certain definite times of year seemed to be critical periods. Seventy-seven per cent of his cases occurred in the spring and fall. If one will follow his own ulcer case histories he will find that in the great majority this seasonal predominance exists.

During these seasons there is a greater variability of the meteorological environment. Thus it would appear that this factor must play an important rôle in the reaction of the unstable individual who is afflicted with an ulcer.

In this connection the report of Preuner[1] on the effect of weather conditions on experimental asthma in guinea pigs is interesting. He found in a statistical study that the induced asthma was not dependent on such meteorological factors as temperature, humidity or atmospheric pressure as long as these factors remained constant, but that during periods of rapid change in weather conditions the average severity could be increased about 50 per cent. The fact that these meteorological factors are thus subject to accurate statistical study in laboratory animals is of basic scientific interest and, as pointed out in the *Journal of the American Medical Association*,[2] the new field of experimental meteorobiology may conceivably assume an important rôle in future therapeutic study.

Clinically, other diseases and symptom complexes exhibiting periodicity are those of the skin, prostate, certain types of asthma and hay fever, sinusitis and the historical shoemakers' tetany. Pulmonary emboli as Peterson and deTakats have shown, are predominantly seasonal in their occurrence. There are also seasonal variations in the calcium, phosphorus and vitamin C levels of the blood. The iodine content of the thyroid gland in animals has been shown to vary markedly with the seasons, as recently brought out by Fenger. These are a few examples demonstrating the seasonal tide.

Experimentally, ulcers have been produced in the stomachs of dogs by the use of pitressin, in the exact location as seen clinically in man. The blood supply to the tissue was diminished through increased tone or actual spasm of both muscle and blood vessels, with subsequent digestion of the involved area producing an ulcer. Time does not permit further examples.

From these facts it can be seen that we are not dealing with an organism that is static and immutable but with an integrated and highly complex mechanism which must adjust itself continuously to the forces in its environment, both external and internal. Meteorological forces such as changes in temperature, humidity, barometric pressure and the intensity of light are the most constant to which the individual must adjust himself.

Dietetic factors such as lack of intake or loss of certain vitamins or minerals play an important part.

It is not reasonable to assume that a constitutionally unstable individual who may be depleted of certain substances or

[1] Preuner, R. Allergiestudien. *Ztschr. f. Hyg. u. Infektionskr.*, 1939, *121*, 559–568.

[2] Current Comment. *J. Am. M. Ass.*, 1939, *113*, 1036.

changed chemically by other factors is going to react emotionally in the same way as another individual who is well buffered in his chemical and constitutional makeup. However, let us not forget the tremendous rôle that emotional disturbances can play producing both psychic and physical disturbances.

I have attempted to present some of the environmental factors which affect the individual, and have brought to your attention two conditions which seem to be local expressions of a system disturbance. The first, a spasm, expressing itself as a dysfunction, and the second, an ulcer, which goes through the stage of dysfunction on to tissue death and digestion.

Fundamentally it would appear that pylorospasm is the result of an autonomic imbalance and that ulcer is an expression of an oxygen lack brought on by diverse environmental factors, both internal and external, in a constitutionally inadequate individual.*

* For discussion see page 841.

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FORMS OF ULCERATIVE COLITIS

CORRELATION OF CLINICAL AND ROENTGENOLOGIC DATA*

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IT BECOMES more and more evident as experience accumulates and as diagnostic criteria become more precise that it is better to use the term "chronic ulcerative colitis" in a broad sense to denote a general clinicopathologic syndrome than to use it in a narrow sense to denote some one of the several specific disease entities in which this syndrome is developed. The term will be used in the broader sense in this paper. The syndrome of chronic ulcerative colitis may develop as a result of infection by one or more of several bacterial and animal parasites, or in association with certain dietary and constitutional deficiencies, or as a result of poisoning with certain chemicals. In medical practice it becomes necessary to distribute cases of chronic ulcerative colitis according to etiologic types, and the first and most fundamental clinical effort is directed at determining the specific etiologic factor responsible for the development of the syndrome, so that a more rational therapy may be instituted.

To determine the relative incidence of the various etiologic types of chronic ulcerative colitis which have come under our observation, and to test the validity of the diagnostic criteria by which we have been assigning our cases into these types, we have undertaken a statistical analysis of the case histories of 500 consecutive patients who came to the Mayo Clinic in the twenty-six months from February, 1933, to April, 1935, and whose clinical records had been entered in our statistical files under the designation of "ulcerative colitis." Bargen, Jackman and Kerr, in a paper entitled "Studies on the life histories of patients with chronic ulcerative colitis," made an analysis of a large series of cases in which the disease was of streptococcic type. It was one of their aims to define the clinical pattern of this type of chronic ulcerative colitis within sharper limits, thus to provide a more reliable guide for future classification of this and closely related intestinal diseases. They deliberately excluded from consideration all cases in which the disease was not clearly of this one type as determined by careful clinical, bacteriologic, proctoscopic and roentgenologic appraisal, as well as those cases in which the disease was proved to be of tuberculous or amebic origin. The group of cases we have selected for study differs from theirs chiefly in that it is a consecutive series and embraces all etiologic types of chronic ulcerative colitis coming to us in a relatively short, but we think a fairly representative, period of time. We chose a series of this kind for several reasons. In the first place, our experience with some of the more rarely encountered types of ulcerative colitis had accumulated sufficiently to enable us to formulate a somewhat more precise set of diagnostic criteria to be applied to them. Secondly, we had observed that the clinical and morphologic manifestations of even the more familiar types of ulcerative colitis varied, at times widely, with stage and virulence of the infectious process, with extent of intestinal involvement, and with presence or absence of complications. Thus, in some instances the manifestations were observed to become more typical at a later time; in others the ultimate diagnosis had to be made on the basis of the response to a more or less specific line of therapy. Our selection of a series of cases

* Read at the Fortieth Annual Meeting, American Roentgen Ray Society, Chicago, Ill., Sept. 19–22, 1939.

TABLE I
DISTRIBUTION AS TO TYPE

Type	Number	Per cent
1	332	66.4
2	17	3.4
3	48	9.6
4	14	2.8
5	78	15.6
6	1	0.2
7	3	0.6
Combined	7	1.4
Total	500	100.0

of this kind with this particular relationship in time to our entire series made it possible to take matters like these into consideration, because we have had the privilege of observing many of the patients on two or more occasions over a period of at least four years.

CLASSIFICATION

On the basis of bacteriologic and parasitologic, pathologic and clinical examinations, it was found that each of the cases of this series could be placed into one of seven types (Table I) which have been designated as follows:

Type 1. Into this group were placed those cases in which the patients had the disease commonly known as "chronic ulcerative colitis," "colitis gravis," "idiopathic ulcerative colitis" and by various other names. Buie and Bargen have suggested the term "thrombo-ulcerative colitis" as a more suitable name for this type of chronic ulcerative colitis. We consider a characteristic streptococcus to be the primary inciting organism. In our experience, this is by far the most commonly encountered type of ulcerative colitis (Table I). Of all the types of ulcerative colitis, it has the most consistent and most typical clinical, pathologic and hence, proctoscopic and roentgenologic manifestations (Tables II and III). The intestinal wall is diffusely involved. Earliest and severest manifestations appear in the rectum and lower segments of the colon. The disease tends to spread diffusely upward until the entire colon, even the lower part of the ileum, becomes involved (Table IV). Because of its relatively very high incidence, 66.4 per cent in this series, and because of the consistency with which its clinical, proctoscopic and roentgenologic manifestations conform to a certain pattern, we are inclined to use this type of ulcerative colitis as a norm and to describe other types chiefly by noting in what respects they differ from it.

Type 2. In this group were placed those cases of chronic ulcerative colitis in which the condition differed pathologically from that of type 1 (thrombo-ulcerative colitis) chiefly in that those segments within reach of the proctosigmoidoscope were not involved in the pathologic process. The existence and extent of the lesion was revealed at the roentgenologic examination (Table IV). The roentgenologic appearance of the diseased intestine may resemble that of any other form of ulcerative colitis very closely, or the diseased intestine may have a different, almost distinctive roentgenologic "look." Involvement may be diffusely spread over the entire colon, not including the rectum and sigmoid, or it may be irregularly distributed with rela-

TABLE II
COMPARISON OF DIAGNOSIS AS MADE BY PROCTOSCOPIC EXAMINATION AND ULTIMATE DIAGNOSIS IN 464 CASES IN WHICH PROCTOSCOPIC EXAMINATION WAS MADE

Type as determined by proctoscopic examination	Total	Type—ultimate diagnosis							
		1	2	3	4	5	6	7	Combined types
1	323	309		6	1	2	1		4
2									
3	48	17		27		3			1
4	1			1					
5	41	2		6	1	30			2
6									
7	3							3	
Negative	48	2	15	6	2	23			
Total	464	330	15	46	4	58	1	3	7

tively normal segments between those severely diseased. No common bacteriologic or other etiologic agent has been determined for this form of ulcerative colitis.

Type 3. In this group were placed those cases of chronic ulcerative colitis in which the lesion was similar in all pathologic respects to that described as type 2, except that those segments within reach of the proctosigmoidoscope were involved either alone or with segments of the colon above this level (Table IV).

The pathologic changes in the last two types of chronic ulcerative colitis present no clinical features by which they may be distinguished from each other consistently, and they are not to be distinguished from each other pathologically except by the distribution of the ulcerative process in the intestine. The division into two types was made chiefly for purposes of study. In ulcerative colitis type 3 a more complete and detailed pathologic picture is made available by the proctosigmoidoscope; in ulcerative colitis type 2, pathologic information is obtained less directly since it is deduced from roentgenologic data, although some detailed pathologic information has been obtained in those relatively few instances in which specimens were made available for study by

TABLE III

COMPARISON OF ROENTGENOLOGIC DIAGNOSIS AND ULTIMATE DIAGNOSIS IN 442 CASES IN WHICH ROENTGENOLOGIC EXAMINATION WAS MADE

Type as determined by roentgenologic examination	Total	Type—ultimate diagnosis							
		1	2	3	4	5	6	7	Combined types
1	261	243	4	8				2	4
2–3	41	3	13	20	1	2		1	1
4	10				10				
5	19	1		2	1	14			1
6	1						1		
7									
Negative	110	65		11	1	32			1
Total	442	312	17	41	13	48	1	3	7

TABLE IV

EXTENT OF LESION AS REVEALED BY ROENTGENOLOGIC EXAMINATION, IN THE VARIOUS TYPES

Extent of lesion	Type									
	1		2		3		4		5	
	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Rectum—sigmoid	25	7.5								
Rectum—splenic flexure	26	7.8								
Rectum—hepatic flexure	28	8.4								
Rectum—cecum	169	51.0								
Cecum			4	23.5			3	21.4	6	7.7
Cecum—ascending colon							4	28.6	4	5.1
Cecum—hepatic flexure			1	5.9	4	8.3				
Cecum—splenic flexure			6	35.4	6	12.5	1	7.1	3	3.8
Cecum—sigmoid			3	17.6						
Scattered distribution			3	17.6	6	12.5				
Entire colon					12	25.0	4	28.6	5	6.4
Rectum—recto-sigmoid					7	14.6				
Rectum					6	12.5				
Negative	65	19.6							34	43.7
No examination	19	5.7			7	14.6	2	14.3	26	33.3
Total	332	100	17	100	48	100	14	100	78	100

surgical removal or at necropsy. In this series there were 65 cases of these two types of ulcerative colitis, a substantial group, representing 13 per cent of the entire series. It is our feeling that the type of ulcerative colitis represented by these 65 cases has largely led to much of the confusion of the real nature of ulcerative colitis in which the precise etiologic factor has been doubtful or in dispute. In 1930, we reported a small group of cases of chronic ulcerative colitis in which the distribution of the ulcerative process in the intestine was atypical. For these we used the designation "regional migratory ulcerative colitis." Some of these would now be classified as type 2 ulcerative colitis, and certain cases of "regional entero-colitis" would also be included in this group at the present time.

Type 4. This group includes those cases of ulcerative colitis in which the disease was considered to be due to infection of the intestine with *Mycobacterium tuberculosis*. Table IV shows the extent and distribution of the pathologic intestinal changes as revealed by roentgenologic examination.

Type 5. This group includes those cases in which the ulcerative colitis was considered to be due to infection with *Endamoeba histolytica*. It includes those cases in which actual organic changes were revealed in the intestine either at proctoscopic or roentgenologic examination, or both, as well as cases in which no such changes were demonstrated. The extent and distribution of the pathologic changes in the intestine as revealed by roentgenologic examination are shown in Table IV.

Type 6. This group includes those cases of atypical ulcerative colitis in which the pathologic and clinical manifestations differ from those of other types. In these cases the disease is considered to be part of the syndrome of one of several forms of dietary insufficiency.

Type 7. This group includes those cases of ulcerative colitis in which the involvement is practically always limited to the rectum and lower part of the sigmoid colon. The etiologic background is considered to be the same as that in cases of lymphogranuloma venereum.

Combined types. In but 7 cases in this series were two etiologic factors considered to be operating simultaneously to produce a mixed type of chronic intestinal infection. In 6 of the 7 cases *Endamoeba histolytica* was found to be present, in the stools, while the clinical and pathologic evidence pointed clearly to the coexistence of type 1 (thrombo-ulcerative) ulcerative colitis.

CLINICAL CONSIDERATION

The allocation of a given case of chronic ulcerative colitis into one of the types enumerated is usually done very readily, but sometimes it becomes a very difficult task. In general it may be said that the diagnosis is made by critical analysis of the history and the findings at physical examination and by correlating these with the objective evidence of intestinal disease as revealed by proctosigmoidoscopic and roentgenologic examination. Buie has contributed particularly vivid descriptions of the pathologic appearances of these ulcerative processes as the proctosigmoidoscope reveals them. He expressed the opinion that certain gross morphologic features are pathognomonic of certain etiologic types of ulcerative colitis. Intimate association with Buie and his colleagues in the Section on Proctology of the Mayo Clinic for many years permits us to confirm the validity of his opinion. The importance of the evidence yielded by expert use of the proctosigmoidoscope and by correct interpretation of the findings in the light of a large experience cannot be estimated too highly. The evidence of the competently performed and carefully interpreted roentgenologic examination ranks next in importance. In certain types of ulcerative colitis the roentgenologic manifestations are only somewhat less definitive than the proctosigmoidoscopic manifestations. Roentgenologic evidence assumes the primary position of importance when characteristic

proctosigmoidoscopic findings are lacking. Frequently, however, roentgenologic and proctosigmoidoscopic diagnoses are found to be in disagreement, and now and then the evidence yielded by one or the other or by both examinations is such that a definite diagnosis is not forthcoming. It is in such instances that the clinician finds that he must pursue new or unusual avenues of inquiry. The history and physical examination assume renewed importance. The results of hematologic examinations, of histologic, cytologic, bacteriologic, and chemical analyses of stools, of specific serologic and immunologic tests, and finally of more or less specific therapeutic tests all are advanced in evidence and critically evaluated.

Although the histories of patients afflicted with these types of ulcerative colitis have, in general, marked degrees of similarity, significant points may often be elicited on the sole basis of which it may be possible to predict the ultimate diagnosis rather accurately. A history of rectal bleeding that has continued for weeks or months but has gradually increased in amount, that has been accompanied by diarrhea which developed insidiously but gradually increased in severity often to the point of being intractable, with remissions and exacerbations of both symptoms, points strongly to the existence of ulcerative colitis type 1 (thrombo-ulcerative). When dysentery develops in a case of pulmonary tuberculosis, if ulcerative colitis of any kind is present it will probably be tuberculous in origin (type 4). The history of a patient with dysentery will often show that he has been in a region where amebic dysentery has been endemic, and this gives an immediate clue as to the possible nature of the difficulty (type 5). The history of a patient with dysentery may also show that he has long subsisted on a diet obviously inadequate; in instances of this kind the clinician will conduct investigations along dietary lines (type 6). In ulcerative colitis type 2 and type 3 the history is just as lacking in distinguishing diagnostic features as are the pathologic manifestations. The onset is usually severe, but may be mild; even though the stools and rectal discharges are not great in number, great depletion may take place rapidly. Disturbances of the upper part of the digestive tract are observed more frequently in this type of ulcerative colitis than in others.

In this series of patients with ulcerative colitis 62 (12.5 per cent) were less than twenty years of age; 305 (61 per cent) were between twenty and forty years of age; 115 (23 per cent) were between forty and sixty years of age; and only 18 (3.5 per cent) were more than sixty years of age. The youngest patient was an infant of fifteen months; the oldest was a man aged seventy-three years. Two hundred and seventy-nine patients (56 per cent) were males.

The cases were analyzed by type with respect to duration, degree of severity, and degree of anemia as indicated by determinations of the amount of hemoglobin in the blood. Patients with ulcerative colitis type 1 (thrombo-ulcerative) in general had symptoms for long periods of time, while patients with ulcerative colitis types 2, 3 and 4 (tuberculous) were ill for relatively short periods of time. In general, the symptoms of all types of ulcerative colitis were of moderate degrees of severity. Severest anemia was observed in cases of ulcerative colitis type 1 (thrombo-ulcerative). This is not a surprising finding since patients with this disease were ill longer and had occasion to suffer greater losses of blood than patients with the other types of ulcerative colitis.

As was pointed out earlier in this paper, the final or ultimate diagnosis in cases of ulcerative colitis is not always made on the occasion of the patient's first consultation with the physician. The diagnosis may be made with relative ease when all findings dovetail into what has become recognized as the typical clinical and pathologic syndrome of one of the better-known types of ulcerative colitis. This is usually the case. Experience with some of

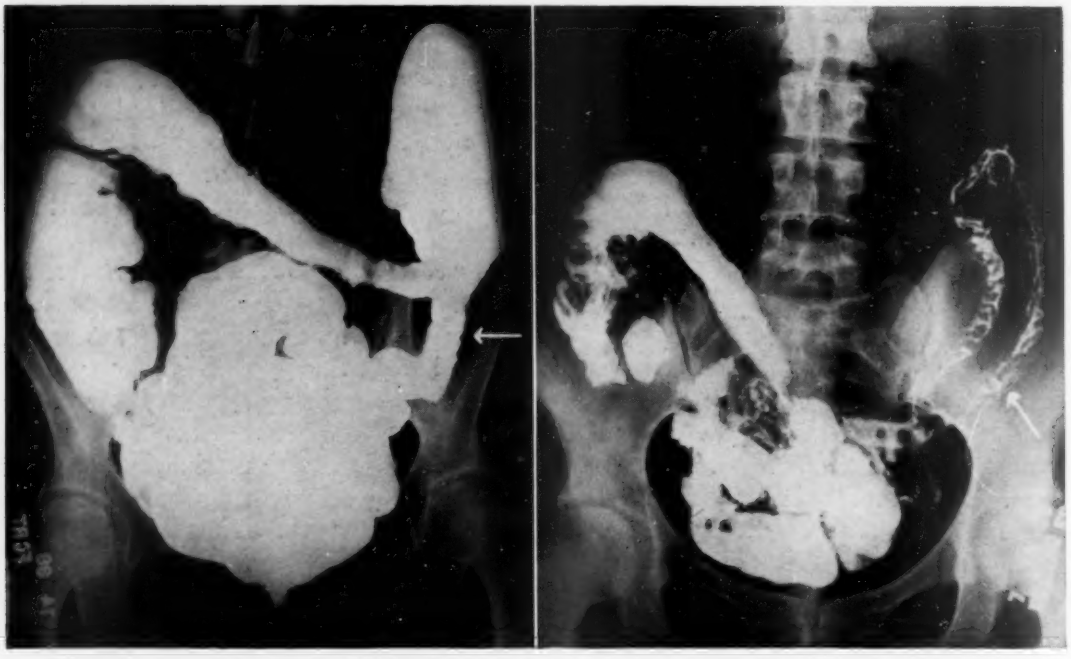

FIG. 1. Ulcerative colitis type 2; involvement confined to transverse colon, including both limbs of hepatic flexure, and to a short segment of descending colon (arrows); results of proctosigmoidoscopic examination negative.

the more rarely encountered forms of ulcerative colitis is so meager that we feel competent to draw but tentative conclusions about them. Sometimes, in all of the forms of ulcerative colitis, the patient is seen at a time when the pathologic process is so destructive that significant and pathognomonic features are effaced. In such instances it may be necessary to delay making the ultimate diagnosis until general and more or less specific therapeutic measures have succeeded in alleviating the acute and fulminating character of the process.

This study has emphasized again that neither the history and physical examination nor any single objective test is sufficient in all instances to provide the final diagnostic word in cases of ulcerative colitis. The final diagnosis is made and proper therapeutic measures are instituted only after all relevant diagnostic data are collected, carefully evaluated and properly correlated.

ROENTGENOLOGIC CONSIDERATION

Since the roentgenologic manifestations of all forms of chronic ulcerative colitis reflect the gross morphologic changes which the pathologic process produces in the size, shape and contour of the part of intestine affected, the roentgenologic diagnosis is expected to be no more determinative than is the diagnosis made after gross pathologic examination. Anatomically, chronic ulcerative colitis of all types produces some degree of narrowing and shortening of the intestine, destructive or productive changes in the intestinal wall and ulceration on the mucosal surface. The intensity of the changes produced varies with such factors as the duration and extent of the disease, its virulence, and the amount of secondary infection. As was pointed out earlier in this paper, certain macroscopic features of the ulcerative process are so distinctive that the etiologic nature of certain forms of ulcerative colitis is often determined accurately by inspection of the mucosal surface of the intestine at proctosigmoidoscopic examination. Many of the particular features used in making the proctologic diagnosis are, however, not elicitable at roentgenologic examination because they are com-

posed of such visual elements as color, the nature and distribution of exudates, and very small differences in size and shape of small mucosal defects. On the other hand, the less delicate macroscopic changes, that is, the gross deformities, are not essentially pathognomonic because the processes by which they have been developed are essentially the same, whatever the cause of the disease. Roentgenologically demonstrable changes in the intestine produced by the ulcerative process are general contraction, which implies narrowing and shortening, productive and destructive changes in the intestinal wall, changes in mobility and flexibility as revealed by roentgenoscopically controlled manipulation, and destruction of the internal surface of the intestine as revealed by changes in the pattern of the mucosal relief. For diagnostic criteria, to be used in distinguishing the forms of ulcerative colitis from each other, the roentgenologic examiner is limited to such roentgenologically recognizable features as the site of earliest and severest involvement, the distribution of the process in the intestine, its methods and direction of extension, the general intensity of the disease, and the roentgenologic findings in other organs which might give a clue to the nature of the intestinal disease. In addition, the experienced observer may discern a peculiar roentgenologic "look" which enables him, intuitively almost, to postulate a diagnosis without being able to offer, to a less experienced roentgenologic observer, very acceptable reasons for doing so.

The roentgenologic manifestations of chronic ulcerative colitis type 1 (thromboulcerative), type 4 (tuberculous), and type 5 (amebic), have been described elsewhere.[6] It is important to emphasize only that, while these have the most consistent roentgenologic syndromes of all forms of ulcerative colitis, in all instances the roentgenologic evidence must be carefully weighed and evaluated, preferably, of course, and sometimes of necessity, in collaboration with the clinician and proctoscopist.

The roentgenologic manifestations of the types of ulcerative colitis which we designated as types 2 and 3 deserve some comment. Review of the roentgenologic findings in these types leaves the impression that no single description could be made

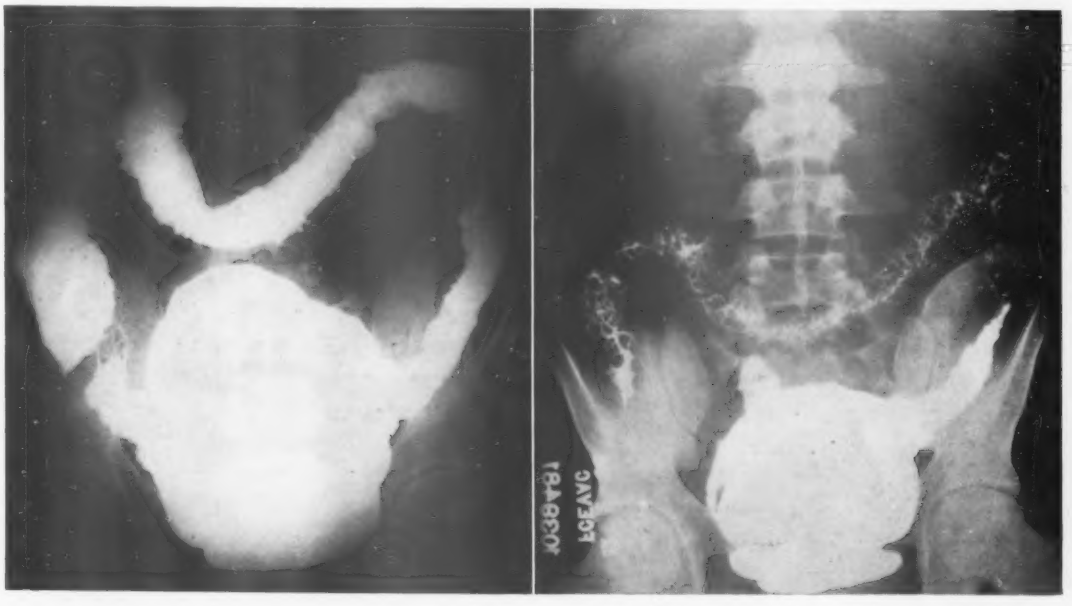

Fig. 2. Ulcerative colitis type 2; diffuse ulcerative colitis involving the entire colon above and including the descending portion; results of proctoscopic examination negative except for a single small rectal polyp; *left*, roentgenogram of colon distended with opaque enema; *right*, after evacuation of opaque enema.

to include all the manifestations in all of the cases. It is possible to divide them into two groups: one in which hyperplastic or productive elements predominate in the roentgenologic picture, and another in which ulcerative or destructive elements predominate. Thus the resemblance to intestinal tuberculosis is obvious; in fact when the ileum and cecum are both involved, a purely roentgenologic distinction denied. Most frequently, however, the roentgenologic appearance of the segments involved with this atypical form of ulcerative colitis has a destructive "look" (Figs. 2 and 3), and with experience a characteristic, irregular development of the process is readily recognized.

The roentgenologic appearance of the colon in the deficiency states (type 6) may superficially resemble that of one of the

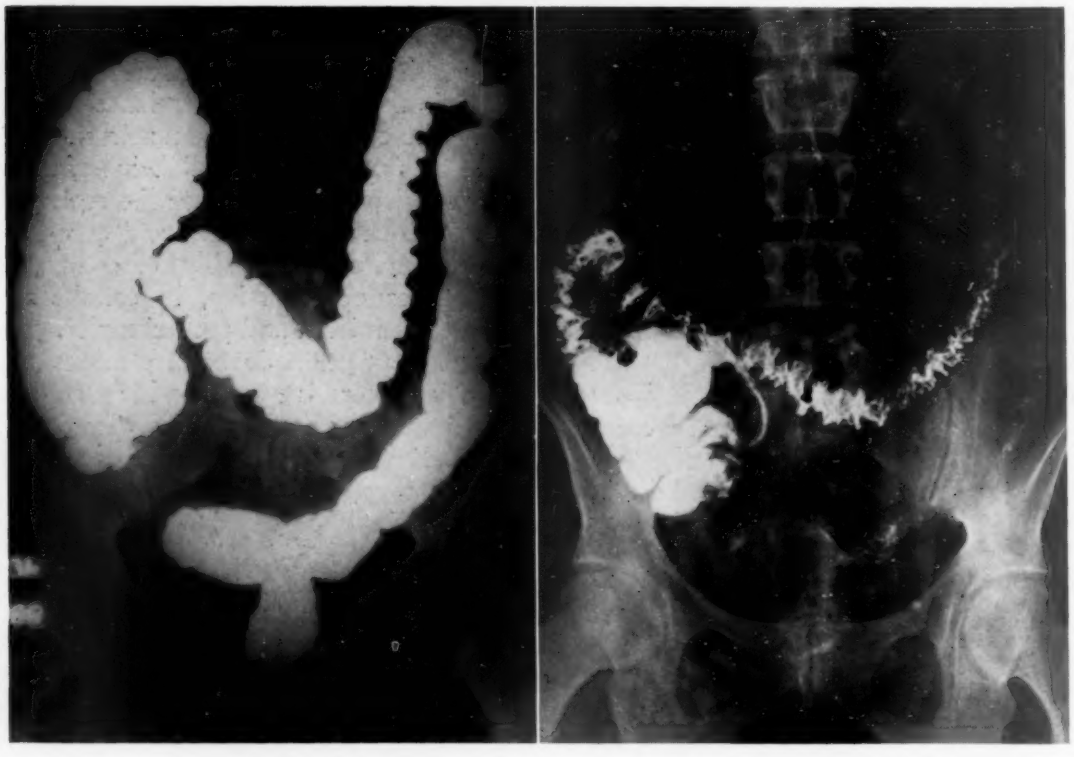

FIG. 3. Type 3 ulcerative proctosigmoiditis at proctoscopic and roentgenologic examination; *left*, roentgenogram of colon distended with opaque enema; *right*, after evacuation of opaque enema.

between tuberculous and non-tuberculous ulcerative colitis cannot be made. If evidence of active pulmonary tuberculosis is elicited, the presumptive diagnosis is evident immediately. The irregular distribution of the lesions in types 2 and 3 is shown in Table II. The roentgenologic appearance may resemble that of type 1 very closely in every respect except the distribution (Fig. 1). That when this occurs, the disease may indeed be of the same etiologic nature as in type 1 cannot be other types of chronic ulcerative colitis, but the resemblance is not, as a rule, marked. Because ulcers, when they have developed, are superficial, and because submucosal infiltration does not take place to a great extent, contraction either in length or in caliber is not observed. The caliber of the intestine tends, as a matter of fact, to be larger than normal. Marked atonicity of the bowel is one of the striking features. Combining with this are a marked reduction in the mucosal relief, an excessive

quantity of abnormal intestinal secretion which is probably responsible for the peculiar distribution of the contrast substance on the mucosal surfaces, and a striking inability of the intestine to contract and expel its contents efficiently. If this form of intestinal change is confused with other forms of ulcerative colitis roentgenologically, it is because the examiner, unfamiliar with the clinical picture, finds himself at a loss to explain his findings on a basis other than an atypical ulcerative colitis. Frequently, in fact, the large intestine is entirely normal in the states of dietary deficiency.

In all the 3 cases of lymphogranuloma venereum (type 7) in this series there were significant roentgenologic findings. The involvement was confined to the rectum and lower part of the sigmoid. These segments were uniformly shortened and narrowed and there were definite changes in the mucosal relief, consisting in a complete absence of relief in the 2 cases in which the disease was designated as ulcerative colitis type 1 (thrombo-ulcerative) at roentgenologic examination (Fig. 4), and a deeply pitted relief pattern in the case in which the disease was classified roentgenologically as type 3 (Fig. 5). Review of these and other cases in our larger series in which lymphopathia venereum has extended from its original site to involve the rectum and lower part of the sigmoid grossly indicates that a fairly typical roentgenologic syndrome might be developed by which at least a presumptive diagnosis of this disease might be rendered by using roentgenologic data alone.[5]

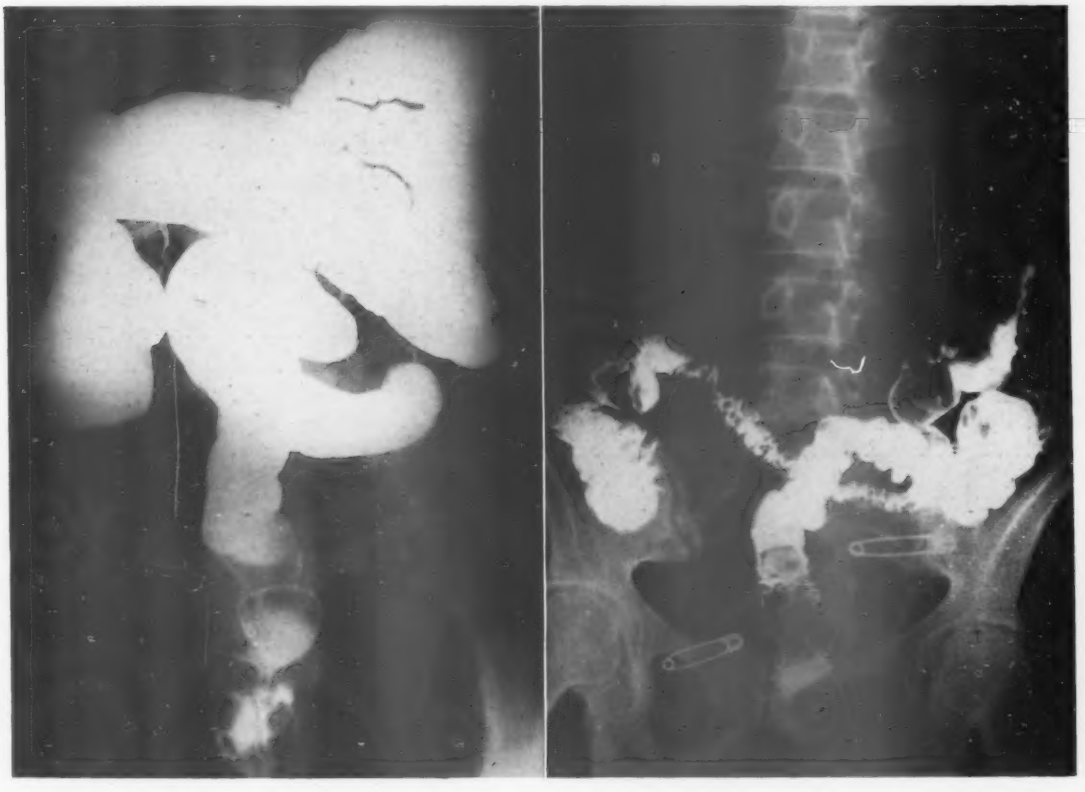

Fig. 4. Ulcerative proctosigmoiditis of lymphogranuloma venereum; Frei test positive; the patient was a Negress, thirty-four years old; she also had a rectovaginal fistula which confuses the roentgenologic picture to some extent; the proctoscopic diagnosis was lymphogranuloma venereum; *left*, roentgenogram of colon distended with opaque enema; *right*, after evacuation of opaque enema.

It is apparent, we believe, that no group

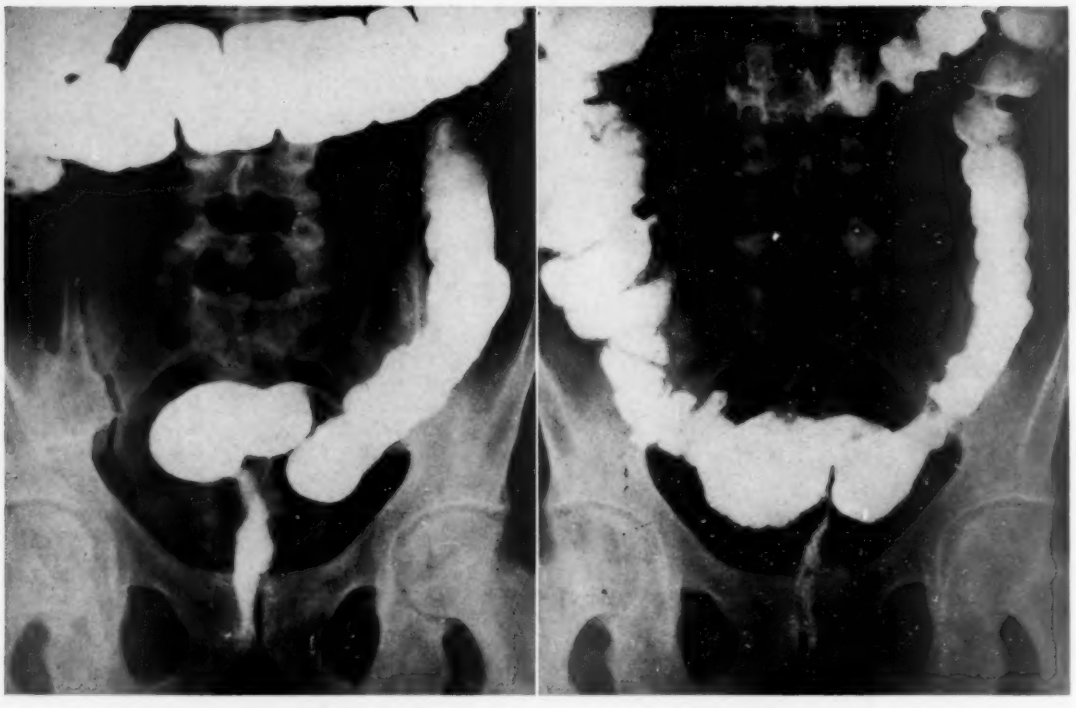

FIG. 5. Lymphogranuloma venereum affecting a white man, thirty-five years old; Frei test positive; proctoscopic diagnosis was lymphogranuloma venereum; *left*, roentgenogram of colon distended with opaque enema; *right*, after evacuation of opaque enema.

of patients requires a more intelligent and complete mobilization of all diagnostic facilities than those with one of the types of ulcerative colitis. No single group of human maladies lends itself better to careful objective analysis than this. The stools are readily examined both with the naked eye and microscopically. The lesions of the rectum and sigmoid are observed directly with the proctosigmoidoscope. The changes produced by the disease above the level of proctosigmoidoscope reach come under observation with roentgenologic methods. Progress in the way of diagnostic refinements continues to be made, and we feel that it is logical to expect that therapeutic advances will not lag far behind.*

* For discussion see page 841.

REFERENCES

1. BARGEN, J. A., and WEBER, H. M. Regional migratory chronic ulcerative colitis. *Surg., Gynec. & Obst.*, 1930, *50*, 964–972.
2. BARGEN, J. A., JACKMAN, R. J., and KERR, J. G. Studies on the life histories of patients with chronic ulcerative colitis (thrombo-ulcerative colitis), with some suggestions for treatment. *Ann. Int. Med.*, 1938, *12*, 339–352.
3. BUIE, L. A. Practical Proctology. W. B. Saunders Company, Philadelphia, 1938, 512 pp.
4. BUIE, L. A., and BARGEN, J. A. Chronic ulcerative colitis; a disease of systemic origin. *J. Am. M. Ass.*, 1933, *101*, 1462–1466.
5. WEBER, H. M. Unpublished data.
6. WEBER, H. M. The roentgenologic identification of commonly encountered chronic ulcerative diseases of the colon. AM. J. ROENTGENOL. & RAD. THERAPY, 1933, *30*, 488–496.

Vol. 43, No. 6

THE SURGICAL TREATMENT OF ULCERATING GASTRIC LESIONS

WITH CORRELATED ROENTGENOLOGIC STUDIES*

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IT IS a great pleasure to have this opportunity to express my appreciation to the members of the American Roentgen Ray Society for their contributions to the diagnosis of surgical lesions of the stomach. Although a carefully taken history and a properly performed physical examination will indicate, in many cases, the nature of the lesion producing the patient's symptoms, confirmatory evidence furnished by roentgenoscopic and roentgenographic examinations not only serves as a visual method of confirming the diagnosis and exact situation of the lesion but in many instances affords an excellent idea not only of its extent, but frequently, the pathologic nature of the lesion. This method of examination, therefore, affords the greatest aid in localizing lesions of the stomach or in eliminating the stomach as the cause of the patient's dyspepsia. It is surprising in some cases, however, how late in the course of the patient's treatment roentgenologic examinations have been made. Treatment is sometimes carried out entirely on the basis of a diagnosis made on a clinical history of dyspepsia not unlike that associated with benign ulceration. On innumerable occasions one encounters patients having carcinoma of the stomach, many of them in advanced stages of the disease, who have been under medical dietary treatment for months, and sometimes years, on the erroneous assumption that benign ulceration of the stomach or duodenum was present. This is largely a result of the fact that the history and early stages of the disease were particularly like those of benign ulceration and prompt symptomatic response was obtained by resorting to frequent feedings and alkalies. Only later, when relief was not obtained by such means, was the roentgenologic examination made showing the malignant nature of the lesion.

In discussing carcinoma of the stomach I have repeatedly emphasized this point, following it with the corollary that no patient should be placed on a medical regimen for what seems to be a benign lesion of the stomach or duodenum without its being first ascertained by roentgenologic examination whether the lesion is in the stomach or duodenum. If it is in the stomach, the possibility that the lesion may be malignant in spite of the fact that it does not appear so on the initial roentgenologic examination should always be kept in mind. This also holds in cases in which the lesion may seem to disappear, roentgenologically, under a medical regimen. Such patients should not be lost sight of until repeated roentgenologic examinations have revealed complete disappearance of the lesion and until the patient's symptoms have been completely relieved. The fact that more than 95 per cent[1] of gastric lesions can be demonstrated by the roentgenologist is a real achievement. The internist and surgeon must nevertheless remember that, with approximately a 5 per cent error in roentgenologic examinations of the stomach, the patient who appears by the clinical history to have a gastric lesion but for whom results of a roentgenologic examination were negative should not be dismissed without the admonition that other roentgenologic examinations be made at intervals of two or three months. Better still,

* Read at the Fortieth Annual Meeting, American Roentgen Ray Society, Chicago, Ill., Sept. 19–22, 1939.

if a competent gastroscopist is present, as should be the case, gastroscopic examination should be combined with repeated roentgenologic examinations in an attempt to ascertain for certain that no intragastric lesion is present.

MALIGNANT GASTRIC LESIONS SIMULATING BENIGN ONES

When roentgenologic examinations demonstrate seeming localization of the lesion in the duodenum, it would seem to be rather conclusive evidence that the lesion is benign, for the first part of the duodenum is one of the rarest sites for primary malignant lesions to develop. However, there is a group of patients in whom ulcerating lesions of the lesser curvature of the stomach, because of associated gastric spasm and interference with gastroduodenal motility, produce roentgenologic data which may be misinterpreted as pyloric or duodenal obstruction. This may lead to the erroneous localization of the lesion in the duodenum when in reality it is in the stomach. The following 3 cases are illustrative.

REPORT OF CASES

CASE I. A woman, aged forty-three, came to The Mayo Clinic on January 6, 1938. For twenty-two years she had had ulcer-like distress and had been following a diet for ulcers since August, 1937. The gallbladder had been removed in 1928 and she had had some relief for a short time following this operation. She complained of fullness after meals and occasionally had experienced pain at night. She had vomited old food on an average of once a week and recently, three times a week. Alkalies and milk gave relief. A roentgenologic diagnosis of duodenal ulcer with obstruction and considerable secondary dilatation of the stomach was made. The patient underwent operation on January 10, 1938, partial gastrectomy with Billroth 1 anastomosis being performed. The lesion was reported by the pathologist to be a Grade 1 colloid adenocarcinoma, situated at the pyloric end of the stomach. No duodenal ulcer could be distinguished. After an uneventful convalescence, the patient was dismissed on January 28, 1938. In a letter dated December 14, 1938, she wrote that she was feeling and sleeping better than in many years, that her appetite was fairly good and that she was able to eat almost all kinds of food.

CASE II. A man, aged fifty, registered at The Clinic on October 6, 1938. He had had epigastric distress after meals for two years, with relief from food never more than 75 per cent of the time. He had had no nausea, vomiting, hematemesis or melena. He had lost 23 pounds (10 kg.) in the past two years. He had been following a diet for ulcers without much relief. Roentgenologic examination of the stomach disclosed a duodenal ulcer with a crater. Gastric analysis revealed anacidity and because of this observation it seemed advisable to perform gastroscopy; this was done on October 11, 1938. However, no lesion could be seen in the stomach to account for the patient's symptoms, although a satisfactory view of the upper portion of the stomach could not be secured because of excessive secretion At operation on October 14, 1938, multiple carcinomas of the stomach were found, and total gastrectomy was performed. There was also marked hemorrhagic gastritis and chronic duodenitis. The patient died on October 19, 1938, of bronchopneumonia.

CASE III. A man, aged fifty-nine, returned to The Clinic on December 6, 1938. In 1909 drainage of his gallbladder had been performed and the opening to his stomach had been dilated. In 1914 partial cholecystectomy and appendectomy had been performed, and on March 15, 1924, cholecystectomy had been performed. Examination of the duodenum at the time of cholecystectomy disclosed a condition that was suspiciously like an ulcer on the anterior wall, but a positive diagnosis of duodenal ulcer could not be made because of the amount of adhesions remaining from the previous operation. For three years before returning to The Clinic in 1938, the patient had had intermittent attacks of epigastric pain two or three hours after meals; this distress was relieved by food and soda. He also had experienced frequent pain at night, with extension to the back. He had occasionally vomited during the spring of 1938 and also about three months before coming to The Clinic. He stated that his stomach felt full after meals and it seemed to require a long time for it to empty. The roentgenologic examination showed a duodenal ulcer and deformity of the stomach situated under the scar of the gallbladder. At operation on

December 16, 1938, carcinoma on a gastric ulcer was found, and partial gastrectomy, with posterior Polya anastomosis and partial duodenectomy, was performed. Chronic gastritis and chronic duodenitis were also present. The patient's convalescence was uneventful and he was dismissed on January 9, 1939.

These 3 cases were the only ones of this type which came to my attention during 1938. I mention this because, although the possibility of error exists, fortunately the condition occurs infrequently. It is a point, however, which I think should be emphasized, especially to the internist who favors the nonsurgical treatment of all duodenal ulcers unless they constitute surgical emergencies.

DIFFERENTIAL DIAGNOSIS OF BENIGN AND MALIGNANT GASTRIC ULCERATION

In the Annual Oration for 1936, delivered before the Medical Society of London, Sir James Walton said, when referring to carcinoma of the stomach secondary to peptic ulceration: "Today the figures of Stewart are generally accepted. . . . Nine and one-half per cent of cases of chronic ulcer become carcinomatous and 17 per cent of cases of carcinoma originate in a chronic ulcer." Quoting further, Walton said: "Clinical criteria are notoriously unreliable . . . . The history of carcinoma in its early stages may also closely resemble that of chronic ulcer, so that an even higher percentage of the cases diagnosed clinically as chronic ulceration become malignant . . . . In early cases the diagnosis of carcinoma may only be possible on microscopic examination, while in the later stages the mass of growth may be so extensive that it is impossible to determine with the naked eye whether the ulcer is primary or secondary. Microscopic examination will nevertheless often reveal characters of the original ulcer."

It seems to me that Walton has concisely stated the case against gastric ulcer from the standpoint of the menace of carcinoma.

When to this statement is added Katsch's figure that a gastric ulcer has a 20 per cent chance of being malignant, it emphasizes the necessity of attempting to differentiate between the benign gastric ulcer and the gastric ulcer with malignant changes. I wish to call your attention particularly to this point because it is by the earlier recognition of malignant changes in such small lesions that we are going to be able not only to increase the number of people having carcinoma of the stomach who can be operated upon, but also, an excellent opportunity will be afforded of prolonging the patient's life and obtaining a cure in such cases by partial gastrectomy. Unfortunately, the wave of enthusiasm which a few years ago was evident in certain parts of the country to advise medical treatment in all cases in which a roentgenologic diagnosis of gastric ulcer was made led to the postponement of necessary operations. In these cases, particularly in those in which the ulcer was large and perforating in character, not only was relief of symptoms temporary but little change was noted in the size of the lesion. In addition, with the passage of time it was found that a few of the lesions had been carcinomatous ulcers and not benign ones. Unfortunately, in some of these cases the delay plus the rapidity of growth of the lesion made surgical removal difficult and in some cases, impossible. Although in the last two or three years the viewpoint regarding the management of such lesions has improved, there are still those physicians who have failed to be impressed by the fact that whereas the report of a malignant gastric ulcer by the competent roentgenologist is usually a correct one, Kirklin has pointed out that the roentgenologic report that a lesion is a gastric ulcer does not exclude its being carcinomatous. On many occasions wherein lesions have been reported preoperatively as being malignant because the meniscus sign-complex of Carman and Kirklin was present, I have thought at operation on the gross appearance of the lesion that it might be benign, only to have the patholo-

FIG. 1. Large, recurring, perforating gastric ulcer situated high on the lesser curvature of the stomach. (Published by permission of the *American Journal of Surgery*.)

gist report it as being malignant on microscopic examination. At The Clinic we assume that every ulcerating lesion of the stomach is malignant until it is proved to be benign.

The medical critics of the surgical treatment of ulcer, in supporting their thesis that medical treatment of all gastric ulcers should be carried out, like to substantiate their argument by saying that less than 10 per cent of the ulcers are malignant or become malignant and that, in view of this fact and the high risk entailed in the removal of the ulcer, medical treatment always should be undertaken. These arguments, it seems to me, are fallacious when it is known that more than 10 per cent of such lesions actually are malignant and when it is considered that the risk of removing either a gastric or duodenal ulcer in the hands of surgeons experienced in gastric surgery is exceedingly low. In point of fact, sixty-two operations were performed for nonperforated gastric ulcer at The Mayo Clinic in 1938, with a mortality rate of 3.2 per cent. Three hundred and forty-three operations were performed for nonperforated duodenal ulcer during the same period, with a mortality rate of 1.2 per cent. Partial gastrectomy was performed for benign lesions of the stomach and duodenum in 215 cases, with a mortality of 2.8 per cent.

There is another lesion, the early recognition of which is important because frequently it contains malignant cells in its periphery, and this lesion is the gastric polyp. The fact that many of these polyps do contain malignant cells in the periphery of the lesion and the fact that the roentgenologist is able to demonstrate the presence of these lesions in most instances when they are no larger than one's fingernail, should lead to their earlier recognition and removal, particularly in those cases in which secondary anemia is present, for many of these polyps produce silent bleeding.

It is a routine at The Clinic to examine the stomach and colon of all patients who have marked anemia, even though the morphologic picture of the blood would seem to indicate that the anemia was of the primary type. It has been a surprise to many of us how frequently bleeding polyps have been demonstrable in these regions in such cases, many of which lesions have been removed surgically, resulting in disappearance of the anemia.

THE OPERABILITY OF GASTRIC LESIONS

Gastric ulcers situated high on the lesser curvature and those situated high on the posterior wall of the stomach are frequently reported, on the basis of roentgenologic examination, to be of questionable accessibility to surgical removal. Their high situation is likely to be considered an additional reason for continuation of medical treatment which has failed to cause healing of the ulcer previously. That all benign gastric lesions are accessible to surgical treatment is, therefore, a point which deserves emphasis. On several occasions, because of the perforating nature of the lesion and its attachment, particularly to the capsule of the pancreas, and because of contraction and fixation of

the stomach in the vicinity of the lesion, the appearance has been that the lesion was higher than it really was.

In a case in which I operated two years ago, a man of sixty-eight years had a large, recurring, perforating gastric ulcer, 3 cm. in diameter, high on the lesser curvature (Fig. 1). No evidence of healing of the ulcer occurred on medical treatment. The reason the ulcer seemed so high was that it had perforated and attached itself to the capsule of the pancreas and to the gastrocolic omentum. When the ulcer was freed from its attachment to the pancreas, it was found that there was a considerable amount of normal stomach above it, which enabled performance of satisfactory partial gastrectomy of the Polya-Balfour type.

Removal of that portion of the lesser curvature which contains a gastric ulcer, as in the Billroth 1 or the Hofmeister-Polya resection, enables the surgeon to preserve a sufficient amount of the body of the stomach, and particularly the greater curvature, for its anastomosis with the duodenum or with the jejunum (Fig. 2*a* and *b*).

In addition to these methods, the transgastric method of removal of some of the ulcers on the posterior wall, at the fundic end of the stomach, has given very good results.

In reviewing the problem of carcinoma of the stomach, Cranston Holman stated: "Up to the present time surgery offers the only satisfactory means of treatment and, as the methods of Billroth and their various modifications are still considered technically adequate, it is doubtful whether in the future any startling advances will be made in the technical approach to curing carcinoma of the stomach." While in general I agree with this opinion, it would appear that, with increasing experience in gastric resection, particularly that for malignant disease of the stomach, the greater the experience of the operator in this field the greater will be the number of cases in which gastric resection will be performed. In some of the American clinics there has been a progressive increase in the percentage of cases in which gastric resections have been performed; or, in other words, greater operability has been attained in some clinics by willingness to

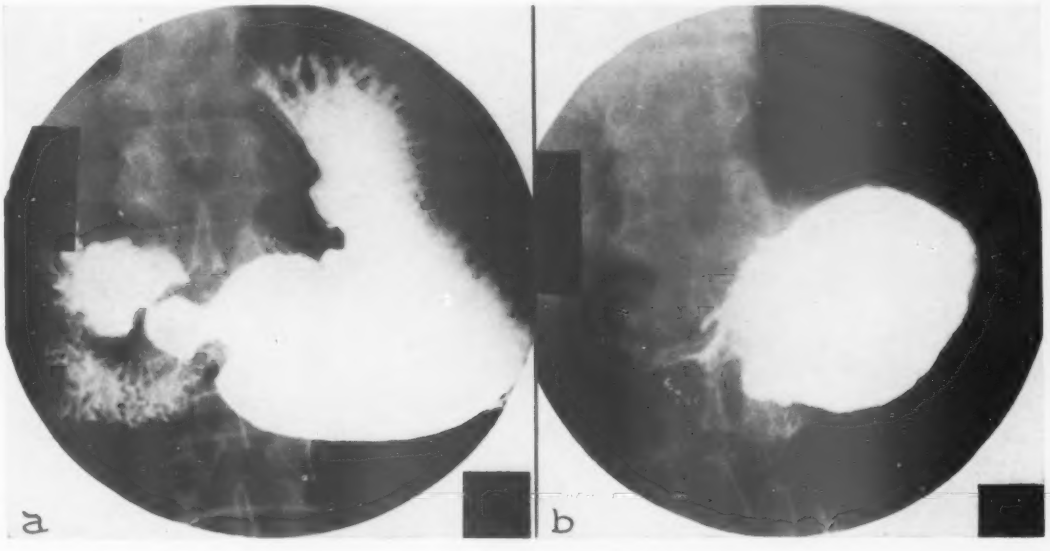

Fig. 2. *a*, perforating gastric ulcer (hemorrhagic) on the lesser curvature; *b*, postoperative roentgenogram following Billroth 1 resection of the stomach and the gastric ulcer. (Published by permission of the *American Journal of Surgery*.)

resect from three-fourths to four-fifths of the stomach without hesitancy when the lesion is confined to the stomach and, in a few cases, even to perform total gastrectomy. Last year at The Mayo Clinic in 251 cases in which operations were performed for malignant neoplasms of the stomach, partial gastrectomy was performed in 124 cases, or an operability rate of 49.4 per cent, with a mortality rate of 13.9 per cent.

In 1937,[8] at the Inter-State Post-Graduate Medical Assembly of North America, in discussing carcinoma of the stomach, I called attention to the fact that the advances made in the previous year in the treatment of carcinoma of the stomach might be attributed in part to: (1) increased operability as result of accepting for exploration all patients having carcinoma of the stomach, provided their general condition does not contraindicate it and provided metastasis cannot be demonstrated (in 1938 at The Mayo Clinic operation was performed for 61.4 per cent of all patients having carcinoma of the stomach), and (2) willingness to perform as extensive a resection as necessary, even to the extent of subtotal or total gastrectomy in order to remove a malignant lesion confined to the stomach or its adjacent glands. [Resections of the stomach were performed on 48.8 per cent of patients having carcinoma of the stomach operated on in 1938; in 1937 the rate for resection was 49.3 per cent and in 1936 it was 45.3 per cent.]

It is apparent, therefore, that not only is a larger group of patients having carcinoma of the stomach being explored but within this larger group a larger number is having partial gastrectomy performed.[7]

On many occasions I have seen malignant lesions of the stomach, which, on roentgenologic examination seem to encroach on the upper third of the stomach, but at operation there was found to be considerably more uninvolved stomach above the lesion than appeared to be the case in the roentgenologic examination. So frequently has this been the case and so extensive have been the resections for malignant lesions of the stomach at The Clinic in the past few years that it seems to me that our roentgenologists have modified their viewpoint regarding operability by indicating as inoperable only those cases in which most of the cardiac end of the stomach is involved. Although this procedure sometimes makes it difficult for the surgeon to explain why he is unable to remove a lesion which the roentgenologist reported as being operable, it accomplishes a far more important purpose in permitting surgical exploration for a larger group of patients, some of whom will be found to have operable lesions.

The corollary of this substantiates the argument that all patients having malignant lesions of the stomach, no matter how extensive, should be given the benefit of abdominal surgical exploration, provided distant metastasis cannot be demonstrated.

It has been our experience at The Clinic that in from 15 to 18 per cent of patients in whom a malignant gastric lesion has been reported to be of doubtful operability or inoperable it was found, on exploration, that the lesion could be, and was, therefore, removed.

A few years ago my assistant, Dr. Norman Thiessen, several of my colleagues, and I[6,7] were interested in carrying out a follow-up study of cases of this type in which three-fifths or more of the stomach had been removed at operation. We found 184 consecutive cases between the years of 1918 and 1931. It was with the greatest satisfaction that we noted that 33 (17.93 per cent) of these patients were living and well without evidence of recurrence five years or more following partial gastrectomy. The preoperative roentgenologic diagnosis in 129 of the 184 cases was "operable," in 40 cases, "operability doubtful," and in 15, "inoperable." Of the 15 patients for whom the preoperative roentgenologic report had been "inoperable" and upon whom partial gastrectomy was performed, 1 patient lived twelve years, 1 lived eight years, and 2 patients lived six

years. Sixteen patients who lived five or more years after operation had had involved lymph nodes at the time of operation. These patients, then, could be considered to be "pure salvage."

SUMMARY AND CONCLUSIONS

Roentgenologic examination of the stomach affords a great aid in recognizing and localizing lesions of the stomach or eliminating the stomach as the cause of the patient's dyspepsia. The supplementary value of the gastroscopic examination as a check on the roentgenologic report, particularly in patients with a clinical history of a gastric lesion but the results of whose roentgenologic examinations have been negative, will serve to decrease the error in the diagnosis of intragastric lesions by these two methods to a minimum.

Since many patients who have carcinoma of the stomach in the early stages have a history suggesting peptic ulcer, it should not be assumed that such patients have benign lesions of the stomach or duodenum until the same is proved by roentgenologic examination and until the presence of an intragastric malignant lesion is excluded. In an occasional case, a malignant gastric ulcer will produce sufficient pylorospasm to lead to the erroneous assumption that the lesion is in the duodenum and is benign, when in reality it is in the stomach and may be malignant. The possibility of this error should always be borne in mind and whenever the question arises, gastroscopic examination would be of great assistance in localizing the lesion in, or excluding it from, the stomach.

Experience has shown that the report by the roentgenologist that a gastric ulcer is malignant is practically always correct, but the report that a gastric ulcer is present and that it is benign does not exclude its being malignant.

Accumulating evidence would seem to indicate that the percentage of gastric ulcers that are malignant as well as the number of malignant lesions which start as gastric ulcers is much nearer 20 per cent than 10 per cent.

In the case of patients who have anemia, roentgenologic examinations of the stomach and colon have frequently shown that a bleeding polyp is the cause of the anemia. Many of these polyps contain malignant cells in their periphery and their early recognition and removal may prevent the development of an extensive malignant lesion. It is a great triumph for the roentgenologists that they can demonstrate polypoid lesions of this type that are as small as 0.5 cm. in diameter.*

REFERENCES

1. Gray, H. K., Balfour, D. C., and Kirklin, B. R. Cancer of the stomach. *Am. J. Cancer*, 1934, *22*, 249–286.
2. Holman, Cranston. The diagnosis of gastric carcinoma and peptic ulcer; the comparative value of various procedures, with special reference to the gastric analysis. *J. Am. M. Ass.*, 1937, *108*, 1383–1385.
3. Katsch. Quoted by Hurst, A. F. Carcinoma of the stomach. *Lancet*, 1937, *2*, 1455.
4. Kirklin, B. R. Roentgenologic distinction of benign from malignant ulcerating lesions of the stomach. *J. Michigan M. Soc.*, 1937, *36*, 453–457.
5. Stewart. Quoted by Walton, ref. 10.
6. Thiessen, N. W. Results of subtotal gastrectomy. *Proc. Staff Meet., Mayo Clin.*, 1935, *10*, 582–584.
7. Walters, Waltman. The treatment of extensive malignant lesions of the stomach. *J. Am. M. Ass.*, 1934, *103*, 1345–1348.
8. Walters, Waltman. Carcinoma of the stomach. *Proc. Inter-State Post-Grad. M. A. North America*, 1937, pp. 86–91.
9. Walters, Waltman, Binger, M. W., and Eusterman, G. B. Gastric lesions of doubtful operability. *Proc. Staff Meet., Mayo Clin.*, 1935, *10*, 584–588.
10. Walton, James. Carcinoma of the stomach. *Lancet*, 1936, *1*, 1101–1107.

* For discussion see page 841.

THE DIFFERENTIAL DIAGNOSIS OF PYLORIC AND PREPYLORIC ULCERATION*

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THE demonstration of ulcerative lesions in the pyloric and prepyloric areas has become increasingly easy due to the improvement of roentgenologic technique but it cannot be truly said that their differential diagnosis has improved in like manner. This area is particularly important because in it occurs a majority of all gastric carcinomas, benign gastric tumors, and cases of gastric syphilis. It is also a favorite location for the occurrence of benign gastric ulcer, spastic phenomena, and hypertrophic pyloric stenosis.

It is now universally accepted that the differentiation between benign and malignant ulceration in this area cannot always be accurately made by means of the roentgen examination alone. We need the help of every clinical aid which is available, and the final diagnosis must of necessity rest upon careful study of serial sections of the resected lesion. It is well known that carcinoma of the pyloric area may simulate benign lesions clinically and may show a considerable amount of relief following the use of medical ulcer therapy. This relief may persist for some months during which time the malignant process continues to progress.

In this study we are limiting ourselves to lesions of the pyloric ring and the prepyloric area within 1 inch of the pylorus. All of the cases to be reported are those in which the lesions have been resected and careful pathological studies made of the ulcerated areas.

While we do not intend to enter into a detailed review of the literature on this subject, it is necessary to refer briefly to several articles in order to more fully outline the subject we wish to discuss. Camp[1] states that in the region of the pylorus we are concerned chiefly with the differential diagnosis of malignant neoplasms, benign ulcer, pylorospasm, syphilis, and hypertrophic pyloric stenosis. He also states that in the pyloric area carcinoma greatly outnumbers benign ulcer, and that prepyloric ulcer has a greater predilection for undergoing malignant degeneration than ulcers elsewhere in the stomach. Holmes and Hampton,[3] in a study of the material from the Massachusetts General Hospital, found that the relative proportion of benign to malignant prepyloric ulcerations was approximately 1 to 12. They believe that any chronic, indurated lesion occurring in the pyloric antrum within 1 inch of the pylorus but not involving it should be considered malignant until proved to be benign. They believe it wise to surgically remove all such lesions rather than to use medical or palliative treatment. Singleton[6] studied the cases of prepyloric ulcer from the Toronto General Hospital. In 7 cases, where the lesion occurred within 1 inch of the pylorus, partial gastrectomy was done and microscopically the lesions in all cases were found to be benign gastric ulcer. He also reported 4 cases of malignant ulcer in the prepyloric segment. In 3 of these the roentgen picture was that of malignant neoplasm. Jensen and Rivers[4] state that it is extremely difficult, in lesions of the pyloric ring, to arrive at an accurate diagnosis even though all means at the disposal of the clinician are utilized. They estimate that in about 15 per cent of cases with pyloric lesions they are unable to be certain that the lesions are not malignant. They therefore recommend surgical exploration for patients who are found to have such deformities.

In the series of cases we are reporting are

* Read at the Fortieth Annual Meeting, American Roentgen Ray Society, Chicago, Ill., Sept. 19–22, 1939.

included those cases of ulceration of the pyloric and prepyloric area which were thought to be roentgenologically benign or which were indeterminate by this means of diagnosis. We have excluded those cases which were obviously malignant as they do not offer the same diagnostic or therapeutic problem.

We have selected 35 cases for this study. All of these patients have had a resection of the pylorus and antrum of the stomach. The specimen has then been studied by serial sections through the ulcerated area so that a final diagnosis is available.

The ages of these patients varied from twenty-six to seventy-three with an average of forty-six years. Ulcer symptoms were complained of by these patients for as long as twenty years with an average of eight years. In practically all these patients medical therapy had been tried for varying periods of time with indifferent success. In a few patients, however, surgery was decided upon immediately because the deformity was of such a nature that we did not feel we could take the responsibility for excluding maligant neoplasm.

The final diagnosis in these 35 cases, arrived at by microscopic sections, is as follows. There were 24 cases of benign peptic ulcer and of these, 16 were located in the prepyloric area, and 8 in the pyloric ring. There were 7 cases of carcinoma of the antrum, 3 cases of chronic gastritis, and 1 case of syphilis of the antrum.

In the 7 cases of carcinoma the preoperative roentgen diagnosis was as follows: Pyloric ulcer, 2 cases; prepyloric ulcer, 2 cases; narrow antrum but not characteristic, 3 cases. The average age of these 7 cases was forty-seven years and as the average age of the cases in the entire series was forty-six years, this was obviously of no value in diagnosis. The follow-up on these 7 cases indicates that 2 patients are alive and well three years after resection, 1 patient is well at twelve months, 1 patient is well at nine months, and 1 patient operated on in 1929 was lost track of. Two of the patients died of recurrence at eighteen and twenty-four month intervals after resection.

As this is primarily a study of those cases which were thought to be benign or questionable from the roentgen studies, it is obvious that the cases which were benign pathologically were diagnosed the same roentgenologically. Our source of error in this type of case was in determining the anatomical location of the ulcer. In a number of cases we could not be sure whether the ulcers were in the prepyloric area or in the pyloric ring.

The 3 cases of gastritis were not characteristic although 1 of these suggested hypertrophy of the pyloric ring. One was obstructed, and 1 had a shadow which was interpreted as an ulcer pocket.

The case of syphilis was diagnosed as an organic lesion possibly syphilis.

Benign Ulceration. In benign ulceration of the pyloric and prepyloric areas there are certain factors which complicate the roentgenologic picture and in many cases becloud the diagnosis. Probably the chief offender is antral and pyloric spasm, which assumes a much more prominent rôle in these areas than elsewhere in the stomach. The antral lumen may be of small diameter and elongated. In these cases we have frequently had difficulty in demonstrating a niche. In the absence of a niche a diagnosis of benign ulcer cannot be made with assurance as other conditions may exactly simulate this picture.

When the niche of a benign ulcer is seen, it is usually small and surrounded by spastic narrowing of the antrum. It may be difficult to show on the film without the aid of pressure technique but is frequently seen by palpation during the roentgenoscopic examination. The anatomical location of the niche is difficult to determine if it occurs in the immediate vicinity of the pylorus and this is complicated if antral spasm is present. A number of cases which we had indexed as pyloric ulcers were found to be in the base of the cap and those cases were eliminated from this study. Cer-

FIG. 1. Ulcer pocket in prepyloric area. Marked antral spasm. Resection. Pathological examination revealed prepyloric benign ulcer.

tain other cases which gave a similar appearance were on the prepyloric side. In some cases of prepyloric ulcer, a flattening of the antrum is seen on the lesser curvature side. In other cases there is a contraction of the longitudinal muscle so that the pyloric opening is apparently displaced upwards along the lesser curvature by the contracture of the lesser curvature. In these instances there is a concomitant bulging of the stomach on the greater curvature side so that the appearance of the excentric position of the pylorus is made more prominent.

In cases of antral spasm without the presence of an ulcer crater one cannot make an accurate diagnosis with certainty. It is safer to report them as ulcerative lesions of undetermined etiology and to recommend progress examinations at intervals of a few weeks while the patient is on a strict ulcer regimen. If the spasm is due solely to a benign peptic ulcer it tends to disappear under this treatment. It is also imperative to rule out lesions in other parts of the stomach that might be causing reflex antral spasm.

In cases where the ulcer pocket is visualized, the appearance of the pocket will sometimes give information which is of aid in making a differential diagnosis. Large, ragged appearing deep pockets with overhanging edges suggest evidence of malignant neoplasm. When the pocket is small with a conical appearance and sharply circumscribed, there is a much greater possibility of the evidence favoring a benign condition.

Antral Carcinoma. We wish to consider here the types of gastric carcinomas which roentgenologically are likely to be confused with benign ulceration. They are usually classified under the heading of

FIG. 2. Pyloric opening occupies an excentric position. Antral spasm. Suggestion of an ulcer pocket. Resection. Pathological examination revealed adenocarcinoma.

malignant gastric ulcer and ulcerating carcinoma.

The malignant gastric ulcers are usually larger than the benign ones and MacCarty has shown that ulcers with a diameter of 2.5 cm. or more are much more likely to be malignant than those of less diameter. The malignant ulcer pocket is often hazy and irregular in its outline. Peristalsis is usually diminished or absent in the vicinity of the ulcer. Ulcers occurring on the greater curvature side are almost invariably malignant and, as stated above, ulcers occurring in the pyloric antrum have a higher percentage of malignant degeneration than those in other portions of the stomach.

Large ulcerating carcinomas have a characteristic filling defect which is familiar to all roengenologists. They also produce thickening of the gastric wall with interference in the peristaltic activity in that area. Small growths of this type are more elusive and sometimes show little or no defect on plain films. Roentgenoscopically they can be discovered by appropriate palpation and especially if the meniscus sign, described by Carman, is seen. Films made with pressure technique will usually demonstrate the lesion on the films. Kirklin[5] considers the slightly raised, overhanging border to be even more significant because of its greater constancy. When pressure is made over it, the ridge displaces the barium and leaves a clear zone around the ulcerated area if the lesion is on the posterior wall, while if the lesion is situated on the lesser curvature the barium in the stomach is displaced away from the ulcer crater. It is easy to see the mechanism of the production of these signs if one examines the surgical specimen and notes the firm thick ridge surrounding the ulcer crater.

Fig. 3. Antral spasm with deformity. Partial obstruction. Resection. Pathological examination revealed chronic gastritis.

Fig. 4. Narrow funnel-shaped antrum. Resection. Pathological examination revealed syphilis with a small ulcer.

Chronic Gastritis. The diagnosis of gas-

tritis is difficult despite the use of all modern methods of diagnosis. A great deal of knowledge of gastritis has been gained by the recent development of the gastroscope and this and the roentgen examination are the most reliable diagnostic agents.

In the antrum gastritis is associated with considerable spasm causing prepyloric narrowing and elongation of the pyloric canal. In most instances, the mucosal folds are present but may be difficult to demonstrate on the film unless pressure methods are used. The spasm of the antrum may be so marked that barium is prevented from filling the antrum for some time after injection of the meal. Hypertrophy of the pyloric muscle is often observed and this may cause concavity in the base of the cap. Mucosal erosions are rarely seen but when visualized are pathognomonic of this disease. They appear as shallow mucosal defects and represent shallow ulcer craters. The demonstration of thick, irregularly hypertrophied folds is an important finding but one that requires skill and caution in the translation of it into terms of pathology.

Gastric Syphilis. These patients are usually in the second to the fourth decades of life. The clinical findings suggest a progressive lesion which may advance to the stage of gastric obstruction. Because of the difficulty in differential diagnosis it may require a laparotomy to exclude the presence of carcinoma.

The roentgen findings are frequently suggestive of syphilis but not always characteristic of it. In most cases there is a definite thickening and infiltration of the wall of the stomach causing a smooth narrowing of the antrum producing a funnel-like appearance. Peristaltic waves do not pass over it. The pylorus is often open but there may be obstruction, depending upon the stage of the disease. No tumor mass is palpable. The narrowed area is apt to be much smoother in outline than the usual filling defect of carcinoma.

Involvement of the antrum, which is by far the most common type, produces the funnel-like deformity described above. When the pars media is involved the stomach often has a dumbbell shape. In other cases the stomach may be converted to a small tubular stomach similar to linitis plastica. One differential point for the roentgenologist is that the patient may have a marked deformity of the stomach but looks reasonably well and does not have the cachetic appearance of the patient who has a similar defect due to carcinoma. At operation the surgeon is likewise struck by the discrepancy between the roentgenologic defect and the anatomic defect. There may be little anatomic change to account for the roentgenologic defect.

While the roentgen examination is not always characteristic of syphilis, we feel that it is usually suggestive of the true etiology. If the patient has other clinical evidence of syphilis it is justifiable to proceed with a course of antisyphilitic treatment before undertaking more radical measures.

DISCUSSION

A study of this series of cases has convinced us that chronic ulcers occurring in the pyloric and prepyloric areas have a greater tendency to become malignant than similar ulcers in the body of the stomach. It is also evident that it is with the greatest difficulty that the differential diagnosis between ulcer and cancer can be made preoperatively. It should be kept in mind, however, that these cases, which were studied, were the ones which either did not respond to medical treatment or were so extensive that a suspicion of malignant neoplasm was present. In our files are many cases with small niches which were observed to heal under a medical regimen and which have remained healed for varying periods of time. Such cases must be checked at intervals and if there is a return of the ulcer it would seem wise to advise resection.

Jensen and Rivers[4] state that in 15 per cent of pyloric ulcers they cannot be certain that a given lesion is not malignant

but do not state the percentage of cases actually found to be malignant. Holmes and Hampton[3] found the relative proportion of benign malignant ulceration in the prepyloric area to be approximately 1 to 12. Singleton[6] reported 7 cases of benign prepyloric ulceration and 4 cases of malignant neoplasm of the same area. It should be noted, however, that 3 of the latter cases were diagnosed as being malignant preoperatively, which type does not belong in the category under consideration here.

In this series of 35 cases there were 24 cases of benign ulceration and 7 cases of malignant neoplasm, or 69 per cent and 20 per cent respectively. In the benign ulcer group 8 were located in the pyloric ring and 16 were located in the prepyloric area. In the malignant group 2 were located in the pyloric area and 5 in the prepyloric area. In addition there were 3 cases of chronic gastritis and 1 case of gastric syphilis.

There are some who object to resection because of the operative mortality but in this series there was only 1 postoperative death, or approximately 3 per cent. This death occurred from pulmonary gangrene one month postoperatively. This operative mortality is far less than the mortality which would have occurred in the cases of carcinoma in this group if they had not been resected early.

SUMMARY

A differential diagnosis between malignant neoplasm and benign ulcer cannot be made in all cases of pyloric and prepyloric ulceration by means of the roentgen examination.

An early diagnosis is very important in lesions occurring in this area, as they are easily resectable while in the localized stage and the percentage of cure is high.

In all such chronic indurated ulcerated lesions there will be a probable occurrence of malignant neoplasm in from 15 to 30 per cent of the cases.

If ulcers in these areas are treated medically they must be regularly checked at short intervals by roentgenologic examination, and resection advised if there is not prompt and sustained disappearance of the lesion.*

REFERENCES

1. Camp, J. D. Roentgenologic significance of pyloric and prepyloric deformities. *Radiology*, 1931, *16*, 847–855.
2. Golden, R. Antral gastritis and spasm. *J. Am. M. Ass.*, 1937, *109*, 1497–1500.
3. Holmes, G. W., and Hampton, A. O. Incidence of carcinoma in certain chronic ulcerating lesions of the stomach. *J. Am. M. Ass.*, 1932, *99*, 905–909.
4. Jensen, R. M., and Rivers, A. B. Carcinoma or ulcer involving the pyloric ring: differential diagnosis. *Proceed. Staff Meet., Mayo Clin.*, 1939, *14*, 1–4.
5. Kirklin, B. R. Roentgenologic distinction of benign from malignant ulcerating lesions of the stomach. *J. Michigan M. Soc.*, 1937, *36*, 453–457.
6. Singleton, A. C. Benign prepyloric ulcer. *Radiology*, 1936, *26*, 198–208.

* For discussion see page 841.

SYPHILIS OF THE STOMACH

WITH A REPORT OF AN UNUSUAL CASE*

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SYPHILIS of the stomach is frequently described as being an extremely rare lesion, yet at least 115 authentic cases have been observed at the Mayo Clinic (Eusterman[8]). Any disease of which that many cases have been observed in one clinic cannot truly be termed as being extremely rare, but it is an uncommon finding.

The paucity of syphilitic involvement of the stomach found at autopsy is frequently stressed, but there are many factors which might account for this. It is hardly ever the cause of death, and unless one is specifically looking for it, the involvement of the stomach may be easily overlooked, as it is not as firm to palpation as is carcinoma.

The most important cause for the belief that syphilitic involvement of the stomach is extremely rare has been the insistence of many writers on pathologic confirmation before accepting the diagnosis. Just why this confirmation should be necessary is not clear when it is not considered necessary before accepting the diagnosis of syphilis of other organs. As there are no histopathologic findings that are pathognomonic of syphilis of the stomach, and as the pathologist rarely can make a positive diagnosis of the condition, it can readily be seen that to insist on this confirmation will exclude almost all of the cases reported in the literature. The microscopic examination is the least accurate of all of the methods of making the diagnosis. The gross pathology of the disease is much more typical than is the histopathology, and the surgeon should be familar with the gross pathology in order to make the diagnosis at the operating table. Frozen sections taken at the time of operation are of no value in making the diagnosis except to exclude the presence of a neoplasm. Pusch[26] states that "in every case one searches in vain for a histopathologic lesion which is absolutely specific for syphilis." The value of the microscopic examination lies in excluding the presence of some specific pathology other than syphilis, and in this it is very valuable.

Some authors have demanded that the *Treponema pallidum* be demonstrated in the tissue. McNee[17] reported a case in which numerous spirochetes were demonstrated in a lesion in the stomach and he concluded that they were the *Treponema pallidum*. It is impossible to differentiate the *Treponema pallidum* from other spirochetes on microscopic examination of tissues. Singer and Dyas[27] assert that the dark field examination is the only means of accurately identifying the *Treponema pallidum* and that it is impossible to do so on stained slides. Spirochetes, indistinguishable from the *Treponema pallidum*, are frequently seen in sections taken from lungs in cases of fusospirochetosis and are also frequently found in ulcerated lesions in the stomach, usually within the zone of bacterial invasion but sometimes seen deeper. Rabbit inoculation of suspensions of macerated lesions is also inconclusive due to the fact that the spirochete of the naturally occurring rabbit spirochetosis cannot be distinguished from the *Treponema pallidum* (Noguchi[22]). It must be remembered that any or all organisms normally, or incidentally, present on the gastric mucosa, including the spirochetal saprophytes (for man) associated with any ulcerative lesion, would be present in the suspension of the macerated gastric lesion (Pusch[26]).

Syphilis of the stomach is most fre-

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quently mistaken for carcinoma, and many of the gastric resections performed on these cases have been done on the erroneous diagnosis of carcinoma.

Most cases occur in the third or fourth decades of life, but several cases have been reported in the fifth and sixth decades, so that the age of the patient cannot definitely be used to exclude the presence of syphilis of the stomach. The case which I will report was sixty-two years of age at the time of the first observation seven years ago.

The symptomatology is proportionate to the extent of the pathology, obstruction and ulceration which exists in the stomach. Many patients give a history typical of gastric ulcer while others will have a history suggestive of carcinoma. There may be pain which may, or may not, be associated with eating and may, or may not, be relieved or aggravated by food. Vomiting is a frequent occurrence and may relieve the pain temporarily. Hemorrhage will occur in about 50 per cent of the cases. In advanced cases in which the volume of the stomach is markedly reduced, there will be difficulty in swallowing solid foods or complete inability to swallow them. The lower end of the esophagus may become dilated due to the diminished volume of the stomach. The patient will lose much weight but is not as ill looking as is the case with carcinoma. There is usually an absence of hydrochloric acid in the gastric secretions and histamine usually fails to stimulate its production. Eusterman[7] and O'Leary[23] found that 20 per cent of the cases at the Mayo Clinic had a palpable tumor, and a definite sense of resistance was noted over the involved area in most cases in which the patients were thin and dehydrated; 27 per cent had other manifestations of the disease; 73 per cent had a positive Wassermann reaction as the only other manifestation of the disease; and 6 per cent had a negative Wassermann reaction.

Gordon[11] reported a case in which he used thorium dioxide injection to rule out the presence of metastases in the liver, as an aid in differentiation between syphilis and carcinoma of the stomach. This procedure I cannot advocate. Carcinoma of the stomach may be present without metastases in the liver so that a negative finding is of no value. The dangers of late sequelae following the use of thorium dioxide have frequently been stressed in the literature and I feel that these outweigh any advantage that may be gained by its use.

GASTROSCOPIC FINDINGS

The advent of the flexible gastroscope is so recent that it has not been used in a sufficient number of cases of syphilis of the stomach to give a complete picture of the findings. I believe that it will be of great value in the future as an aid in the differential diagnosis between syphilis and carcinoma of the stomach. This examination should be of particular value in cases in which ulcerations are present.

No specific findings have been observed in all cases. The mucosa may appear red flecked and rough with thick swollen folds and hypertrophic changes. Gutzeit and Teitge[12] state that cases of syphilis with primary lesions and with skin eruptions show nothing on gastroscopic examination or only a mild superficial catarrh. The treated and healed syphilitic patients showed superficial catarrh with atrophic changes, sometimes atrophic gastritis, rarely hypertrophic gastritis, more often a swollen condition of the mucosa. In latent syphilis a smooth condition of the mucosa was seen, regardless of whether the patient had, or had not, received treatment, and in tabes a similar condition, with hypertonicity (or contracture). Their conclusion was that the tendency in syphilis, where any change in gastric mucosa occurs, is toward the atrophic state.

Moutier[21] divides the cases into those showing tumor (gumma) formation and leaving a localized scar on healing; ulcerative forms, single or multiple, also on healing leaving scars with more contrac-

ture or distortion of the stomach (hourglass); and those showing a generalized gastritis, often hemorrhagic, resulting in atresia by submucosal involvement. Carey and Ylvisaker[3] report a case with their observations during treatment and after interruption of these treatments.

PATHOLOGY

There are no pathognomonic findings in the microscopic or macroscopic examination of syphilis of the stomach. The gumma is the classical lesion of syphilis but rarely, if ever, is found in the stomach. Gummatoid areas may sometimes be found which will strongly suggest the nature of the pathology, but usually even these will be absent. The most common finding is a granulomatous thickening and induration of the wall of the stomach. The induration is pliable and is not hard, gritty, granular or friable as is the case in carcinoma. This pliability is due to the marked edematous character of the submucosa which is thickened out of all proportion to the thickening of the other layers of the stomach. In addition to the edema the usual features of a chronic inflammatory process are seen such as fibrous tissue proliferation, local and diffuse lymphocytic and plasma cell aggregations, with few polymorphonuclear cells, the infiltration being especially perivascular. These changes will be found throughout the wall of the stomach in the involved areas, but will be most marked in the submucosa. Occasionally gummatous areas with epithelioid cell and giant cell centers and lymphocytic and fibroblastic peripheries will be found. These lesions are not typical gummata and there are no criteria by which they may be definitely distinguished from tubercles. Much has been said concerning involvement of arterioles and venules leading to obliterative vasculitis, and it is claimed that these may play a part in the mechanism of necrosis and ulceration, but these features may be seen in any inflammatory process of long duration.

The histopathology depends upon the area from which the section was taken. In cicatricial areas fibrous tissue changes will predominate; if taken from an area showing ulceration, the usual findings of chronic ulceration will be present except that the ulcer will be more shallow and more irregular in outline than in benign peptic ulcer. Occasionally the luetic ulceration will extend as deep as the peptic ulcer.

The chief value in the microscopic examination is in excluding the presence of a neoplasm or some other specific pathology, and one must not expect the pathologist to confirm the diagnosis from the slides alone as it rarely can be done, and one must not be deterred from making a diagnosis of syphilis of the stomach, provided he has sufficient evidence, by the lack of this confirmation.

The macroscopic findings are much more typical of syphilitic involvement of the stomach than are the microscopic findings, and in most cases the macroscopic findings will be sufficiently typical to make, or strongly suggest, the correct diagnosis. For this reason the surgeon should be familiar with the gross pathology so that he may recognize it at the operating table. Meyer and Singer[19] have given a detailed description of the findings at operation, and for those interested a thorough study of their article is suggested. For a brief description of these findings I will quote some of their comment and summary as follows:

> The responsibility of recognizing the presence of syphilis of the stomach logically falls on the surgeon. The features that serve to distinguish syphilis of the stomach from carcinoma, which is most closely simulated, are as follows: there is a striking disparity in many cases between the extent of the lesion as determined roentgenologically and the extent as observed operatively by palpation. *Whereas in carcinoma one generally finds at laparotomy a more extensive involvement than the X-ray picture indicates, in syphilis of the stomach there is a surprising paucity or complete absence of changes as determined by palpation.* The common lesion of gastric syphilis is not a spherical prominence as

in a tumor, gummatous or neoplastic, but is a flat infiltrate that leads to a plaque-like thickening of the gastric wall. When thin, the infiltrate is readily overlooked. When thick, its relatively soft consistency and pliability distinguish it from carcinoma. On cross section the increase is seen to be due to an edematous fibrous tissue located chiefly in the submucosa. Inspection of the interior of the stomach generally discloses one or more superficial serpiginous ulcers involving a large plateau formed by the infiltrate. The base of the syphilitic ulcer, contrary to the peptic variety, is situated at a higher level than the normal mucous membrane. Fibrous and edematous thickening of the serosa and adhesions, when present, suggest an inflammatory rather than a neoplastic lesion. Associated syphilitic changes that may be detected during the course of the operation include hepatic, intestinal and splenic syphilis. Of these, the co-existence in the liver of gummas, deep stellate scars or sub-total destruction of the left lobe is of greatest aid in the recognition of the type of gastric disease present.

ROENTGEN FINDINGS

As the roentgen findings of syphilis of the stomach have been described fully by Moore and Aurelius,[20] and others, only a brief review of them will be given here.

Three varieties of syphilitic involvement of the stomach have been described: (1) gastritis; (2) ulcer, and (3) gummatous hyperplasia. Syphilitic gastritis may occur during the secondary stage of the disease but cannot be detected roentgenologically. It has been claimed that many simple round gastric ulcers are due to syphilis but this lacks confirmation. Practically all of the reported cases of syphilis of the stomach fall into the third variety: diffuse gummatous infiltration and fibrosis with thickening and contraction of the gastric wall. The mucosa over the involved area frequently shows single or multiple shallow irregular ulcerations. Occasionally the ulcerations may extend very deep and may even perforate.

The location of the area of involvement has been given by Moore and Aurelius[20] as prepyloric 70 per cent, median or hour-glass 22 per cent and, diffuse 8 per cent. In the median or hour-glass type the prepyloric and the cardiac portions are uninvolved and the lesion is situated in the middle third of the stomach. In this type there is a smooth annular constriction which will give an hour-glass defect, or more commonly the defect will be more extensive so that it assumes a dumb-bell shape more than an hour-glass. A notable feature in most of the cases is the great length of this constriction in contradistinction to the typical hour-glass deformity seen associated with benign gastric ulcer. The typical hour-glass defect may, however, be seen in some cases due to syphilis. Instead of having an annular constriction as described above there may be involvement of only the greater curvature of the stomach. This will be well shown in the case which I will report. There may be a relatively smooth filling defect involving the greater curvature in the middle third of the stomach and there may be an ulceration in this filling defect (Fig. 1).

In the prepyloric type, almost without exception, the defect in gastric contour is concentric and rather symmetrical. The contraction is usually pronounced with the lumen narrowed progressively toward the pylorus resulting in a spicular form of the barium shadow, but in some cases it is of tubular shape with constant dimensions. Regardless of the length of the defect, the lumen pursues a straight, or fairly direct course in contradistinction to the markedly tortuous course usually found in carcinoma.

Only 8 per cent of the cases fall into the third group with such diffuse involvement that little remains of the stomach. In reality, I believe that this group is merely the end stage of the prepyloric group and that if a case of the prepyloric group remains untreated it will progress until the entire stomach will become involved, resulting in marked contraction and diminution in size. The transition from the prepyloric to the diffuse is well shown in my case (Figs. 2 and 3). In all cases the contraction is obvious but varies in degree

with some so extensive that only a narrow smooth canal is left, with the cardia reduced to a very small pouch. In this type the barium column may show some delay in entering the stomach and the lower esophagus will show some dilatation due to this, but the esophagus itself is practically never involved by extension of the process from the stomach. The barium passes very rapidly through the stomach and, due to the gaping pylorus, the duodenal cap will appear to be larger than normal, but this is more apparent than real.

If an ulceration is present, the niche will usually not penetrate beyond the normal limit of the gastric lumen as it does with benign gastric ulcer, but will be seen to involve the filling defect in a manner similar to that seen in an ulcerating carcinoma. Peristalsis is absent in the involved area and is seldom seen in the uninvolved areas. The gastric rugae are obliterated and the gastric wall is less pliable than normal on palpation. If a tumor can be palpated it usually will be much less prominent than the size of the filling defect would indicate, and this is a very important point in differentiating between syphilis and carcinoma of the stomach. This absence of a palpable mass, notwithstanding the presence of a gross and constant filling defect, has been emphasized more than any other sign and merits the stress it has received.

Following antisyphilitic therapy it may be seen that the lesion will completely disappear, but on subsequent examination at a later date the filling defect may be seen to have recurred due to scar tissue formation as a result of the healing process. In many other cases, and in all cases showing extensive involvement, no change will be noted in the roentgenological findings in spite of pronounced clinical improvement.

DIAGNOSIS

There are no pathognomonic findings in syphilis of the stomach. The diagnosis must be made by a consideration of all available data. Many rules have been laid down in the literature as requirements which must be fulfilled before a diagnosis can be made, but in no case will all of these requirements be found. No set rules can be laid down for the diagnosis of the disease. Usually the hardest part in making the diagnosis is to consider the possibility of the presence of a syphilitic lesion in the stomach. Of course, the diagnosis of syphilis of the stomach cannot be made if the possibility of the disease is not considered. Once the possibility is considered, the diagnosis will not prove to be very difficult after consideration of all of the data. The surgeon can frequently make the diagnosis at the operating table; the roentgenologist can make the diagnosis in many cases, especially if he considers the obvious clinical differences between patients with carcinoma and those with syphilis, and in many other cases he will render valuable aid to the clinician by suggesting the possibility of syphilis; the pathologist can practically never make the diagnosis just from histological examination.

Eusterman and Balfour[9] assert that "in all cases of syphilis in which a demonstrable gastric lesion is present, regardless of the roentgenologic type or extent of the lesion, the condition should be regarded as syphilitic until it is proved to be otherwise."

The typical patient with gastric cancer is beyond forty years of age, looks gravely ill, is cachectic and has a palpable tumor corresponding in size and location to the roentgenologic deformity. The typical patient with gastris syphilis is less than forty, is thin but not weak or markedly ill, is not cachectic and has no palpable tumor mass in relation to the filling defect. Symmetrical narrowing of the prepyloric segment without a palpable tumor should always suggest the possibility of syphilis. The disease is to be considered when a patient has a lesion resembling scirrhous carcinoma, but is relatively young.

TREATMENT

Antisyphilitic treatment should be instituted immediately in all cases except those with marked obstructive symptoms which demand immediate surgical relief. In all cases of dumb-bell constriction there will probably be so much scar tissue present that antisyphilitic treatment will cause no anatomic restoration and these cases must be treated surgically. In many cases antisyphilitic treatment will cause a disappearance of the gastric lesion with a return to normal in gastric contour. In some of these cases, even though there may have been complete anatomic restoration, there may later develop obstruction due to scar tissue formation and these patients will then have to be treated surgically for relief from the obstruction.

CASE REPORT

R. W., white male, aged sixty-two, was referred to the hospital for roentgen examination of the stomach, by Dr. S. W. Mooring.

His family and past histories are relatively unimportant

About one year previous to his coming to this hospital he began to have attacks of pain in the abdomen. These attacks rapidly grew worse and at times were severe enough to necessitate his leaving his work and going to bed for an entire day. At other times the pain was less severe and of shorter duration. He vomited occasionally at first and this rapidly increased in severity until he began to vomit practically everything that was eaten. There was no relation between eating and the vomiting. There was a rapid loss of weight. His average weight at the onset of his illness was 158 pounds. At the end of six months his weight was 145 pounds. At this time (August, 1932), he consulted the physicians in another hospital and a roentgen examination of his stomach was performed. This examination revealed a smooth filling defect on the greater curvature of the stomach with its lower margin about 3 inches from the pylorus (Fig. 1). In the center of this defect there was a definite ulceration, but this ulceration did not extend beyond the normal limit of the gastric outline. No mass could be palpated. A diagnosis of carcinoma of the stomach was made and he was advised to undergo an operation, but this he refused.

Fig. 1. August 2, 1932. Note filling defect, with ulceration, on the greater curvature of the stomach.

The vomiting continued and he continued to lose weight. He continued to eat solid foods but by now this always caused vomiting and he put himself on a diet of raw eggs and goat's milk.

He was re-examined at the same hospital on April 12, 1933, eight months after the original examination. Ten days after this examination he consulted his physician in this city and was referred to this hospital for roentgen examination. This revealed that the filling defect, seen at the first examination, had disappeared but there was a constant narrowing of the lower third of the stomach. Peristalsis did not pass over this area. There was a smooth defect on the greater curvature in the middle third of the stomach and from this defect small, smooth projections could be seen to extend beyond the limit of the defect (Fig. 2). No mass could be palapted. I felt that the lesion was very atypical of carcinoma and requested a re-examination after one week. This re-examination confirmed the previous findings and I finally concluded that it was a carcinoma. I did not consider syphilis, although the picture was very typical of this disease. At that time I also did not have the films available which were taken at the oth-

FIG. 2. April 12, 1933. The diffuse narrowing of the lower half of the stomach is well shown. The duodenal cap is not shown on this film. The irregularity on the greater curvature in the middle third is very atypical of carcinoma.

er hospital and had no way in which to make a comparison with his previous findings. Operation was advised and again was refused by the patient. He continued to lose weight but continued to work until August, 1933, at which time he was retired on a pension.

There was very little change except for a continued loss of weight and in February, 1935 (three years after onset of the illness) he was admitted to this hospital where he remained twenty-four days and was discharged at his own request. No roentgen examination was done.

In January, 1936, he returned for roentgen examination. He had continued to lose weight and still vomited at times. His diet was entirely liquid and this he was forced to drink very slowly. Roentgen examination (Fig. 3) revealed a definite delay at the lower end of the esophagus with some dilatation of this part of the esophagus. The stomach was markedly contracted and shortened. The cardia was irregular in shape. Peristalsis was absent. There was no palpable mass. No mucosal relief could be seen. The stomach emptied rapidly through the gaping pylorus. The channel through which the barium passed was rather smooth in outline. The duodenal cap filled quickly and appeared to be large, but actually it was of normal size although its diameter was definitely greater than that of the stomach. The condition was thought to be due to an extensive scirrhous carcinoma and no treatment was advised.

He was next observed in April, 1938 (almost six years after onset of symptoms), and roentgen examination revealed no appreciable change since the previous examination (Fig. 4). He had lost more weight, which now was only about 80 pounds. This represented a loss of about 75 pounds during his illness. Due to his good general condition, in spite of the great loss of weight, and in view of no change in the roentgen findings in the stonach, it was thought that the condition was due to syphilis instead of carcinoma. A Hinton test was then done and was reported as being strongly positive for

FIG. 3. January 22, 1936. The stomach shows extreme contraction. *E*, esophagus; *S*, stomach; and *D*, duodenum.

syphilis. He was to be given antisyphilitic treatment by his local physician but did not report to him for the treatments.

On December 19, 1938, he was brought to the hospital in an ambulance due to his weak condition. He was very emaciated. The urine examination was negative. The red blood count was 2,460,000 and the white blood count was 5,700. The hemoglobin was 46 per cent. Physical examination revealed a very emaciated man. The pupils reacted sluggishly to light and accommodation. No masses were palpable in the abdomen. No other abnormal finding was noted. Antisyphilitic treatment was started and continued during his stay in the hospital. He was discharged from the hospital on February 20, 1939. His general condition was greatly improved. He had gained 14 pounds in weight and was much stronger. The red blood count was 2,690,000 and the hemoglobin was 52 per cent.

He returned to his home and continued to receive antisyphilitic treatments.

In April, 1939, he returned for a re-examination of his stomach. He had continued to gain strength and weight and he now weighed 111 pounds (a gain of 31 pounds since beginning of the antisyphilitic treatment). His general condition was excellent. Roentgen examination revealed no change in the findings in the stomach (Fig. 5).

Fig. 5. April 5, 1939. No change can be noted following antisyphilitic treatment. The apparent enlargement of the duodenal cap is well shown.

Fig. 4. April 9, 1938. No appreciable change since the previous examination.

On August 17, 1939, he was re-admitted to the hospital in a very poor condition. He was semidelirious and no interval history could be obtained. He had lost much weight and he vomited practically everything that he took. He remained in this condition for five days, at which time an infection of one side of his face developed. This rapidly spread to the other side and he died on the seventh day following his admission. Through the strenuous efforts of Dr. E. F. Greene permission for a postmortem examination was granted.

The report of the postmortem examination, performed by Dr. F. L. Burnett of Boston, is as follows: The body is that of a prematurely old man who is greatly emaciated. The skin is clean, the subcutaneous fat greatly reduced,

FIG. 6. August, 1939. The stomach is open showing the mucosa and the marked thickening of the gastric wall. The stomach measured 12 cm. in length and 5 cm. in its greatest width at postmortem examination.

but the muscle is of a good color. The omentum forms a thin veil over the abdominal contents. The stomach is very greatly reduced in size and measures 12 cm. in length and 5 cm. in its greatest width (Fig. 6). It is constricted in its mesial portion to form some diverticula. It has a capacity of about 65 cc. The wall is of a uniform thickness and measures about 5 to 6 mm. but forms some diverticula of 4 cc. capacity or less. The mucosa is slightly discolored, especially about the openings of the diverticula. Masses cannot be found in the intestinal walls. The liver does not appear reduced in size, but on the anterior surface there is a small, light colored area about 1 cm. in diameter. The markings are definite but the cut surface has a greenish-brown color. The gallbladder is free of stones and is filled with a thin, yellowish-green fluid. The pancreas, spleen, and adrenals do not appear abnormal. The pelves of the kidneys are dilated and the markings of the cortex are definite. There are firm fibrous adhesions at the apex of the left pleural cavity but the lung is soft. There is an area of consolidation in the posterior portion of the right lung. The heart is not enlarged, the muscle is of good color, and the valves are not abnormal. The aorta is not dilated and the intima is smooth. There are no masses in the mediastinum. Microscopic examination revealed no important findings in the organs exclusive of the stomach. No evidence of a malignant tumor could be found.

The stomach was sent to the Department of Pathology of the Massachusetts General Hospital in Boston and the report of Dr. Benjamin Castleman is as follows: The microscopic examination shows scattered groups of lymphocytes and plasma cells, very often surrounding small vessels throughout the muscularis. In some areas between muscle fibers there are groups of epithelioid-like cells with giant cells. The findings are quite consistent with syphilis.

SUMMARY

Syphilitic involvement of the stomach occurs more frequently than is realized, although it is not a common finding.

The diagnosis is made only after consideration of all of the available data. It is most frequently mistaken for carcinoma and the failure to consider it as a possibility is very often the reason for an incorrect diagnosis. There are no pathognomonic findings.

The pathologist is unable to make the diagnosis in most cases and the value of this examination lies in excluding other pathology.

The clinical, pathological, gastroscopic, and roentgen findings are given and a case is reported showing the progressive changes from early to very extensive involvement of the stomach.

REFERENCES

1. Cabot Case Record No. 21182. *New England J. Med.*, 1935, *212*, 849.
2. Cabot Case Record No. 23451. *New England J. Med.*, 1937, *217*, 787.
3. CAREY, J. B., and YLVISAKER, R. S. Gastroscopic observations of syphilis of the stomach. *Ann. Int. Med*, 1938, *12*, 544–550.
4. CARNS, M. L. Syphilis and carcinoma of the stomach. *Wisconsin M. J.*, 1936, *35*, 725.
5. EDIE, E. B. Syphilis of the stomach. *Pennsylvania M. J.*, 1933, *36*, 586.
6. ESTES, W. L., JR. Syphilis of the stomach. *Am. J. Surg.*, 1933, *20*, 366–377.
7. EUSTERMAN, G. B. Gastric syphilis; observations based on 93 cases. *J. Am. M. Ass.*, 1931, *96*, 173–179.
8. EUSTERMAN, G. B. Personal communication, May, 1939.
9. EUSTERMAN, G. B., and BALFOUR, D. C. The Stomach and Duodenum. W. B. Saunders Co., Philadelphia, 1935.
10. FINNEY, J. O. Syphilis of the stomach. *South. M. J.*, 1937, *30*, 1058–1062.
11. GORDON, A. M. Syphilis vs. carcinoma of the stomach—thorium dioxide injection. *J. Iowa M. Soc.*, 1936, *26*, 674–676.

12. Gutzeit and Teitge. Quoted by Carey and Ylvisaker, ref. 3.
13. Hartwell, J. A. Syphilis of the stomach. *Ann. Surg.*, 1925, *81*, 767–790.
14. Kaplan, B. A case of gastric syphilis simulating carcinoma of the stomach. *New England J. Med.*, 1933, *209*, 1270–1274.
15. LeWald, L. T. Roentgen diagnosis of gastric syphilis. *J. Am. M. Ass.*, 1931, *96*, 179–183.
16. Mayer, H. J. Syphilis of the stomach. *Am. J. Digest. Dis. & Nutrition*, 1937, *4*, 503–507.
17. McNee, J. W. Syphilis of the stomach. *Quart. J. Med.*, 1922, *15*, 215–226.
18. Merrill, A. S. Syphilis of the stomach, with a study of ten probable cases. Am. J. Roentgenol. & Rad. Therapy, 1924, *12*, 444–453.
19. Meyer, K. A., and Singer, H. A. Syphilis of the stomach. *Arch. Surg.*, 1933, *26*, 443–464.
20. Moore, A. B., and Aurelius, J. R. Roentgenologic manifestations in 87 cases of gastric syphilis. Am. J. Roentgenol. & Rad. Therapy, 1928, *19*, 425–432.
21. Moutier, F. Quoted by Carey and Ylvisaker, ref. 3.
22. Noguchi. Quoted by Pusch, ref. 26.
23. O'Leary, P. A. Gastric syphilis; data accumulated from 89 cases. *Am. J. Surg.*, 1931, *11*, 286–293.
24. Priestley, J. T., and Walters, W. Indications for operation in gastric syphilis. *Surg., Gynec. & Obst.*, 1934, *58*, 1030–1035.
25. Pusch, L. C. Ulcerative syphilitic lesions of the stomach—pathological anatomy of 4 cases. *Virginia M. Monthly*, 1933, *60*, 227–232.
26. Pusch, L. C. Syphilis of the stomach. *Internat. Clin.*, 1935, *1*, 56–67.
27. Singer, H. A., and Dyas, F. G. Syphilis of the stomach. *Arch. Int. Med.*, 1928, *42*, 718–734.
28. Sproull, J. Discussion of the occurrence of benign ulcer on the greater curvature. Am. J. Roentgenol. & Rad. Therapy, 1931, *25*, 464–473.
29. Vest, W. E. Gastric syphilis. *West Virginia M. J.*, 1933, *29*, 249–256.
30. Widen, A. Case of visceral syphilis operated upon twice—with an interval of 26 years—because of a suspected cancer of the stomach. *Acta dermat.-venereol.*, 1937, *18*, 216–223.
31. Williams, C. Syphilis of the gastrointestinal tract. *Am. J. Surg.*, 1934, *24*, 834–853.

DISCUSSION OF PAPERS BY DRS. LAING, WEBER AND BARGEN, WALTERS, DOUB, AND MCPEAK

Dr. H. E. Mock, Chicago. First I want to thank all the essayists for sending their papers to me, but I was told that I was to limit my discussion to Dr. Walters' paper only. There is so much meat in his paper that I hate to turn to the criticism of it, on which I wish to speak from the standpoint of too much operation of gastric ulcers.

First I should like to show some slides to emphasize what he said about papillomata. (Slide) This small one was diagnosed by Dr. J. Sagel, at Methodist Hospital, Gary. On the surface when I operated was this bleeding area accounting for the marked anemia that the man had. The pathologist pointed out to me that this might undergo sarcomatous degeneration. It is four years now and there are no signs of it yet.

(Slides) The next one is a very large fibropapilloma. The first one was on the greater curvature and, as you see, this is on the lesser curvature. It was removed by the transgastric route, a rather wide base taken off, and the posterior wall repaired. The pathologist here called it benign. One year later this patient went to another hospital in Chicago and a diagnosis of carcinoma was made without any biopsy, but I think she has metastatic sarcoma from this papilloma, a condition that we must bear in mind in these papillomata.

I want to add my opinion concerning the operability of carcinomas. I think that every lesion of the stomach diagnosed as carcinoma should be explored and, as Dr. Walters says, the removal of many of these inoperable carcinomas is worthy of great praise.

Twenty and thirty years ago a bitter battle waged between Sippy and his followers and the surgeons of the country. Many of you remember those famous meetings when they would argue over this subject of gastric ulcers, and the internists won out to the point that most of us were swayed over at least to try the medical management of these lesions.

Dr. Walters refers to this period when he states: "Unfortunately a wave of enthusiasm to advise medical treatment in all cases in which a roentgenological diagnosis of gastric ulcer was made led to the postponing of necessary operations." Personally, I think this was a very fortunate wave of enthusiasm and one which has been wholeheartedly accepted by the majority of the surgeons of the country. During these thirty years literally hundreds of thousands of patients have received medical treatment for gastric and duodenal ulcers. I dare say in this audience there are at least ten who have had treatment for ulcers. Many of these patients had the benefit of excellent roentgeno-

logical diagnosis and really had the ulcers, but a very high percentage were diagnosed on symptoms and clinical history alone or by very inadequate roentgen films and faulty interpretation of the same.

We must remember that the manufacturers' agents have been very active for more than thirty years in selling one or more roentgen-ray outfits in every community of the land. The supply of really competent roentgenologists for at least half of that time was very small and still is insufficient to cover the country. Unquestionably a high percentage of so-called ulcers were erroneously diagnosed and never existed. Medical treatment was not dangerous, but if wholesale surgery for these cases had become the rule one of the darkest chapters in the history of our profession would have been written.

No one has greater respect for the ability of Dr. Walters than I have. If I get a cancer, there is where I am going. However, I cannot agree with his premise that because 17 per cent of all gastric ulcers eventually become malignant, all ulcers should be resected either locally or by gastric resection. He implies this when he states: "At The Clinic we assume that every ulcerating lesion of the stomach is malignant until proven to be benign." If he had added "either by roentgen-ray, therapeutic test or those needing it by exploration," I would agree with him.

Tuesday, at the Wisconsin State Medical meeting, I heard another great authority state, "Any patient in the cancer age, who has digestive disturbances that do not readily yield to medical and dietary management should be explored and a biopsy diagnosis made."

I do not believe that any of us who teach surgery or any of you who teach roentgenology, whose opinions have great influence with the average surgeon or roentgenologist throughout the country, can afford to take such a radical attitude toward the operative treatment of all ulcers.

An operative rate for gastric resections of 3.2 per cent, and even of 5.6 per cent as reported in another clinic, is exceptional. Mortality rates of 11 per cent or more have been reported. It will be much higher than this in the hands of the occasional operator; therefore, I feel that the death rate from needless surgery on benign ulcers would probably be far greater than the number saved by the early discovery of cancer in even 20 per cent of the ulcers.

What are the facts, not in the great clinics of the country where the more serious cases naturally drift, but out in the field where people in every walk of life depend upon local facilities? Let us take a very large city and an average size city for examples. Dr. Jacob Sagel, of the Methodist Hospital in Gary, told me that whereas he diagnoses many gastric and duodenal ulcers in the course of a year and whereas he has succeeded in having the management and course of the ulcer carefully followed and rechecked by roentgen examination, yet he is positive that not more than 3 per cent of the cases studied have been diagnosed as or proved to be malignant. He lives with his doctors and his patients and would soon know if he were missing 6.5 per cent of gastric cancers.

Dr. Clarence F. G. Brown has been in charge of the gastrointestinal clinic at St. Luke's Hospital for fifteen years. The Sunday morning follow-up dispensary run by this clinic averages 80 to 100 patients. Full roentgenologic facilities are afforded by Dr. Jenkinson. He states, "In a long-time observation in our clinic (fifteen years) only 3 to 4 per cent of the gastric lesions are or become malignant. This amounts to about the same end-result as routine universal operation and the individual lives longer and less expensively without surgery."

In every other respect Dr Walters' paper is a milestone and a guide in the management of gastric malignancies. Internists, surgeons and roentgenologists must cooperate to secure better diagnosis and better follow-up of gastric ulcers. If symptoms persist after adequate medical management of six weeks, the roentgen study should be repeated. As long as evidence of the ulcer exists it should be rechecked every six months and if, in spite of treatment, it shows signs of increasing in size or deformity, it should be explored. Every gastric cancer should be explored for many may prove to be operable, or a benign granuloma may be found which careful biopsy alone can differentiate from a cancer.

Finally, I wish to reëmphasize what Dr. Walters has stated concerning fibropapillomata of the stomach. They are silent bleeders often. They are easily overlooked. They tend in time to undergo sarcomatous changes.

DR. B. R. KIRKLIN, Rochester, Minn. All roentgenologists will share my gratification at Dr. Laing's and Dr. Walters' high appraisal of roentgen examination for the diagnosis of gas-

tric disease. Whether the roentgenologist shall have an opportunity to examine the patient who has a gastric lesion rests on the clinician as a primary responsibility. When this opportunity is granted, a great share of responsibility for disclosing and identifying the lesion is transferred to the roentgenologist, and I am glad to hear that in the estimation of others he is adequately fulfilling his duty. Likewise, I believe that all roentgenologists will heartily approve and appreciate Dr. Walters' warning that roentgenologic methods, or rather those who apply them, are not infallible. Roentgenologists themselves have repeatedly stressed this fact and welcome its reiteration. By directing attention to three similar diagnostic errors that occurred at the Clinic last year Dr. Walters has again shown that occasionally prepyloric cancer can be confounded with duodenal ulcer by the roentgenologist. With interest stimulated by his paper, I have canvassed the statistics of the Section on Roentgenology of the Clinic for the entire year of 1938, and I believe these figures are fairly representative of the results obtained by most roentgenologists. During that year 229 patients, all of whom had been examined roentgenologically, were found at operation to have gastric cancer. Positive report that a lesion existed was made in 225 cases, or 98.3 per cent. In 4 cases the roentgenologist failed to discern any lesion. In 184 cases (80 per cent) the disease was definitely diagnosed as cancer. To these may be added 11 cases in which the lesion was suspected to be malignant and so reported, so that 85 per cent accuracy may reasonably be claimed. In no instance in which the roentgenologic diagnosis was cancer did cancer fail to be found. Among 31 cases in which cancer was not named specifically, the diagnosis was, variously, diffuse hypertrophic gastritis (in a stomach that had been resected), polyp or polyps, ulcer, ulcerating lesion, and lesion at the outlet with or without obstruction. Added to these were the 3 cases diagnosed as duodenal ulcer. I feel that few of these errors or incomplete diagnoses were culpable. Although apparently benign polyps usually are partly malignant the fact can be determined only by microscopic examination. Occasionally ulcers that appear both roentgenologically and macroscopically to be benign, prove to be malignant. The roentgenologic differential diagnosis of lesions near the pylorus is notoriously difficult, as Dr. Doub has pointed out so clearly, and often it is wiser to refrain from attempting to predict their exact nature. The diagnosis of hypertrophic gastritis and those of duodenal ulcer were misleading, and as roentgenologists are human they will probably continue to make such errors occasionally. Certainly it is sometimes impossible to determine accurately whether a lesion is on the duodenal or the gastric side of the pylorus, and clinicians as well as roentgenologists should be keenly conscious of the fact.

My own experience conforms with Dr. Doub's conclusion that ulcers in the prepyloric segment, like those on the posterior wall or greater curvature, are more likely to prove malignant than ulcers situated elsewhere in the stomach.

With Dr. McPeak I agree heartily that there are no pathognomonic roentgenologic signs of gastric syphilis, and that the diagnosis must rest on a correlation of all available evidence. At best the diagnosis is precarious, for often it is almost impossible to distinguish gastric syphilis from scirrhous carcinoma, and I feel that, even when the patient is known to be syphilitic, surgical exploration of his gastric lesion should not be delayed too long by therapeutic tests to determine the character of the lesion.

Dr. Walters (closing). I am particularly glad to have had Dr. Mock mention the disadvantages of the viewpoint that all patients who have gastric ulcers should be operated on. Such was not my intent in the paragraph in my paper in which I said that at the Clinic we regard all gastric ulcers as being malignant until they are proved otherwise, that is, until proved to be benign.

Now what methods are there of proving that a "gastric ulcer" diagnosed roentgenologically is benign or malignant? There are none. Disappearance of the niche from the roentgenogram or on fluoroscopic examination can be accomplished by invasion of the base of the ulcer by the carcinomatous process, as Schindler has demonstrated gastroscopically. Time and again I have seen patients who seemed to have benign gastric ulcers, which at operation were found to be ulcerating carcinomas. In some of these cases under medical treatment the niche has disappeared from view roentgenologically, symptoms have subsided and blood has disappeared from the stool, but the patient has been operated on later and carcinoma of the stomach found at the site of the seemingly benign ulcer.

If we are going to improve our results, in the

treatment of carcinoma of the stomach (I state it this way because the surgeon and the internist are dependent on the roentgenologist to identify the site of the lesion), all must remember that the fluoroscopic appearance of a benign gastric ulcer does not always exclude its being an ulcerating carcinoma. Until the time arrives when roentgenologic data are available to make the differential diagnosis which will prove the ulcer benign, all should accept the viewpoint that an ulcer of the stomach may be malignant.

When the ulcer is small, the symptoms are of short duration and the patient is young, certainly no surgeon with any knowledge of gastric pathology and gastric surgery is going to advise an operation without every attempt being made to heal the lesion medically. Furthermore, the conscientious surgeon is not going to operate on the large group of patients who have medium-sized gastric ulcers without the complications of hemorrhage or perforation and who have never been given the benefit of a trial of a medical regimen. At the Clinic, patients who do not have such complicating factors are put in the hospital on a medical regimen for three weeks. If at the end of that time the ulcer has disappeared, the symptoms have disappeared, and the blood has disappeared from the stool, the patient is permitted to go home, but he is instructed that he must be kept under the observation of his physician and roentgenologist and must have examinations of his stomach every three months for two years. This is done to exclude the possibility that the ulcer instead of healing has been the site of an extension of the carcinomatous process in its border which has obliterated the crater of the ulcer or that granulation tissue has only temporarily filled in the crater of the ulcer. Should recurrence of the ulcer take place surgical removal should be advised.

The most important thing that I can bring to the roentgenologist is first a plea for the earlier recognition of malignant gastric lesions, some of which begin in polyps, others in ulcers or lesions which look like ulcers and which may be carcinomas and second that the roentgenographic report of "gastric ulcer" does not exclude the possibility that the lesion may be malignant.

Vol. 43, No. 6

ANEURYSMS OF THE ASCENDING AORTA, AORTIC ARCH AND INNOMINATE ARTERY*

A CLINICAL, ANATOMICAL AND ROENTGENOLOGICAL STUDY

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DURING the past few years, we have been impressed by the frequency with which aneurysms of the aorta are either overlooked or confused with other chest pathology. The most frequent errors in diagnosis are those concerned with pulmonary tuberculosis, asthma, chronic bronchitis, congestive heart failure, mediastinal neoplasm, pleurisy, angina pectoris, and carcinoma of the esophagus. From a purely clinical standpoint, it is easy to appreciate why such errors arise, since these conditions may produce symptoms similar to those caused by aneurysms of the aorta. We have felt that every suspected chest condition, from whatever cause, should be subjected to careful roentgenoscopic and roentgenologic study and that this closer cooperation between clinician and roentgenologist, where the roentgenologist acts in a consulting capacity, will result in more accurate diagnosis.

It would be well to emphasize that not all aneurysms of the aorta are accessible to roentgen study. The exceptions are represented by the type arising from the sinuses of Valsalva, but even these, as we have pointed out,[1] have certain roentgenological characteristics which should at least raise a suspicion of their presence if the condition is an obscure one involving the root of the aorta. Another type of aneurysm which gives considerable difficulty is the small pouch type which develops either from the convexity of the arch and points in a cephalic direction or from the concavity of the arch and points in a caudal direction. Even here the roentgenologist may be of great assistance.

Aneurysms of the aorta may be divided into intrapericardial, sometimes called "aneurysms of symptoms"; and extracardiac, often called "aneurysms of physical signs." Those of the intrapericardial type involve the sinuses of Valsalva and are often prone to rupture before manifesting marked physical signs, unless complicated by aortic regurgitation; then the symptoms are those of syphilitic aortitis and the two offer considerable difficulty in differential diagnosis. The extracardiac type of aneurysm might well be considered as a space-taking intrathoracic lesion, and, since these aneurysms usually displace and compress neighboring anatomical structures, they nearly always produce definite physical signs. The clinical findings, however, in many of our cases were not so definite or reliable as the literature might lead one to believe. In fact, we believe that there are no classical pathognomonic symptoms and physical signs of aortic aneurysms and, while the diagnosis is very often clinically correct, the services of the roentgenologist are of inestimable aid in confirming or ruling out the presence of such a lesion.

In this study, we shall include aneurysms of the innominate artery because, from our experience, we believe that these aneurysms involve the arch of the aorta in their destructive process just as aneurysms arising from the posterior or the posteroinferior portions of the arch tend to involve the orifice of the innominate artery in their destructive process.

While a few aneurysms of the aorta may be caused by atherosclerosis, mycotic implantation and other ill-defined infections, it is the consensus of students of the subject that at least 95 per cent of these lesions arise directly from syphilitic aortitis,

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and our discussion will be confined to this group.

ANEURYSMS OF THE ASCENDING AORTA

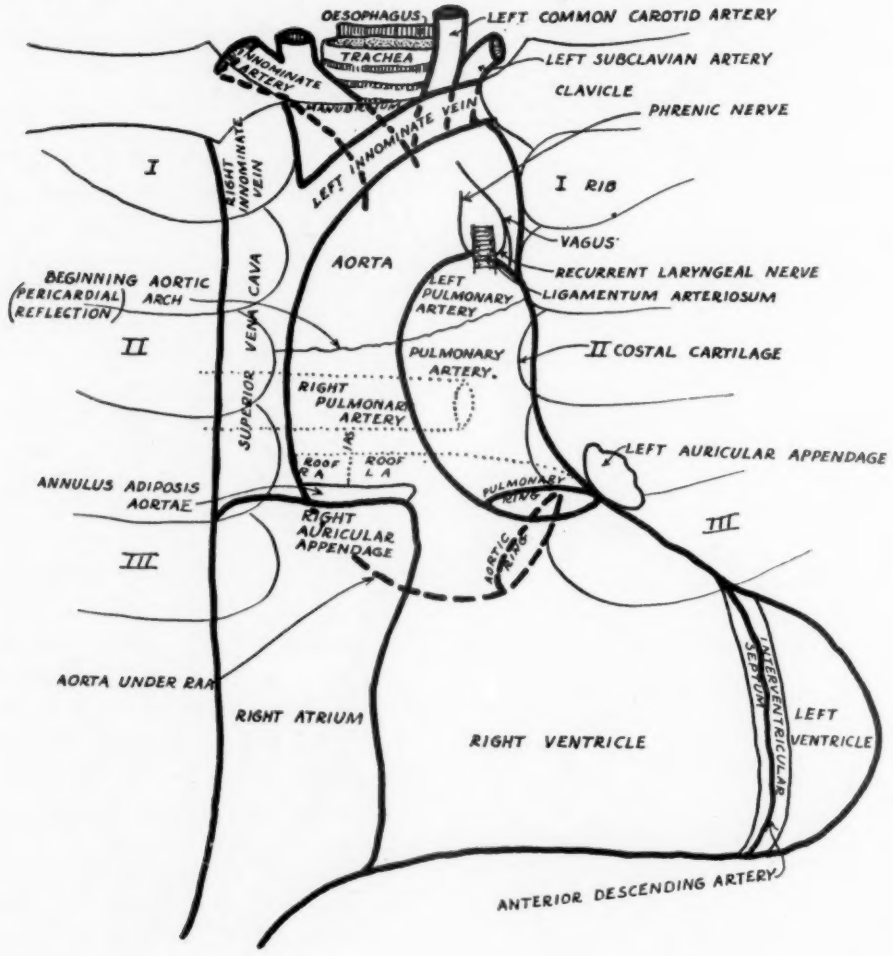
Aneurysms of the initial or the intracardiac portion of the ascending aorta produce perplexing physical signs, and roentgenological findings and in the past have received scant consideration. Their anatomical relations are complex and have been fully covered in our previous communication.[1] We offer here a slightly different classification of aneurysms of the ascending aorta and the aortic arch.

A. Intrapericardial aneurysms: These intracardiac aneurysms, aneurysms of the aortic sinuses, or the sinuses of Valsalva, occur just above the aortic ring and are located at the proximal 1.5 cm. of the ascending aorta.

FIGURE 1

ASCENDING AND ARCH OF AORTA AND RELATED STRUCTURES

ANTERIOR VIEW



ROOF R A – ROOF RIGHT ATRIUM
ROOF L A – ROOF LEFT ATRIUM
I A S – INTERATRIAL SEPTUM

B. Extracardiac aneurysms: These involve the distal 4.5 cm. of the ascending aorta, which ends at the pericardial reflection. The physical signs and symptoms are dependent on the relation to the intrapericardial and the extrapericardial neighboring structures. Rupture would produce a hemopericardium.

Clinical Anatomical Relations. Figures 1 and 2, showing the ascending aorta and the aortic arch, have been prepared from our own dissections of many autopsy specimens, and reference to these is necessary for an understanding of what happens in aneurysms of this portion of the aorta. The blood vessels coming off directly from it are drawn with heavy lines. In front of these are the upper sternum and the chondrosternal junctions, indicated by light lines. Structures posterior to the aorta are shown by light dots. The termination of the ascending aorta and the beginning of the aortic arch are shown by a wavy line, marking the pericardial reflection.

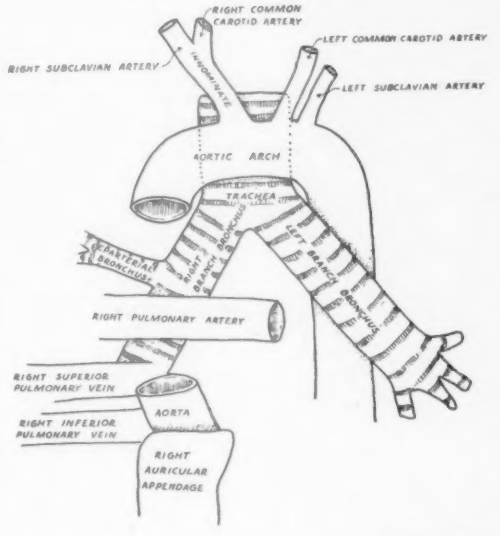
The clinical anatomy may be better understood by dividing this portion of the aorta into the proximal and the terminal portions of the extracardiac aorta:

A. The proximal portion of the extracardiac aorta is covered by the right auricular appendage, the underlying aorta being indicated by a broken-dash line. To the right, on a posterior plane, is the superior vena cava. To the left is the aortic pulmonary septum, separating the aorta and the pulmonary artery. In front is the sternum in the region of the third chondrosternal articulation. Posteriorly, will be found from right to left the roof of the right atrium (*R.A.*), the upper border of the interatrial septum (*I.A.S.*), and the roof of the left atrium (*L.A.*).

B. The terminal portion of the extracardiac aorta begins at the level of the upper border of the right auricular appendage, frequently indicated by a fatty ring on the anterior aorta, annulus adiposis aortae, which we have not found previously described. In Figure 2, this portion of the aorta is cut away to show the posterior relations, which are the structures entering into the formation of the root of the right lung. From below upwards, are the right pulmonary veins, the right pulmonary artery, and the right eparterial bronchus, respectively. In general, the ascending aorta is related: anteriorly, to the right half of the upper sternum; laterally, to the supracardiac vessels (superior vena cava and pulmonary artery); and, posteriorly, to the great transverse sinus and the structures entering into the hilum of the right lung.

FIGURE 2

TERMINAL PORTION OF ASCENDING AORTA CUT AWAY TO SHOW POSTERIOR RELATIONS



ANEURYSMS OF THE AORTIC ARCH

Clinical Anatomical Relations. In the consideration of these lesions, innominate artery aneurysms will be included and the terminal arch will be extended to include the beginning of the descending aorta which lies in front of the left half of the body of the fifth thoracic vertebra and behind the left stem bronchus. Figure 3 is a

FIGURE 3

POSTERIOR VIEW OF AORTA AND RELATED STRUCTURES

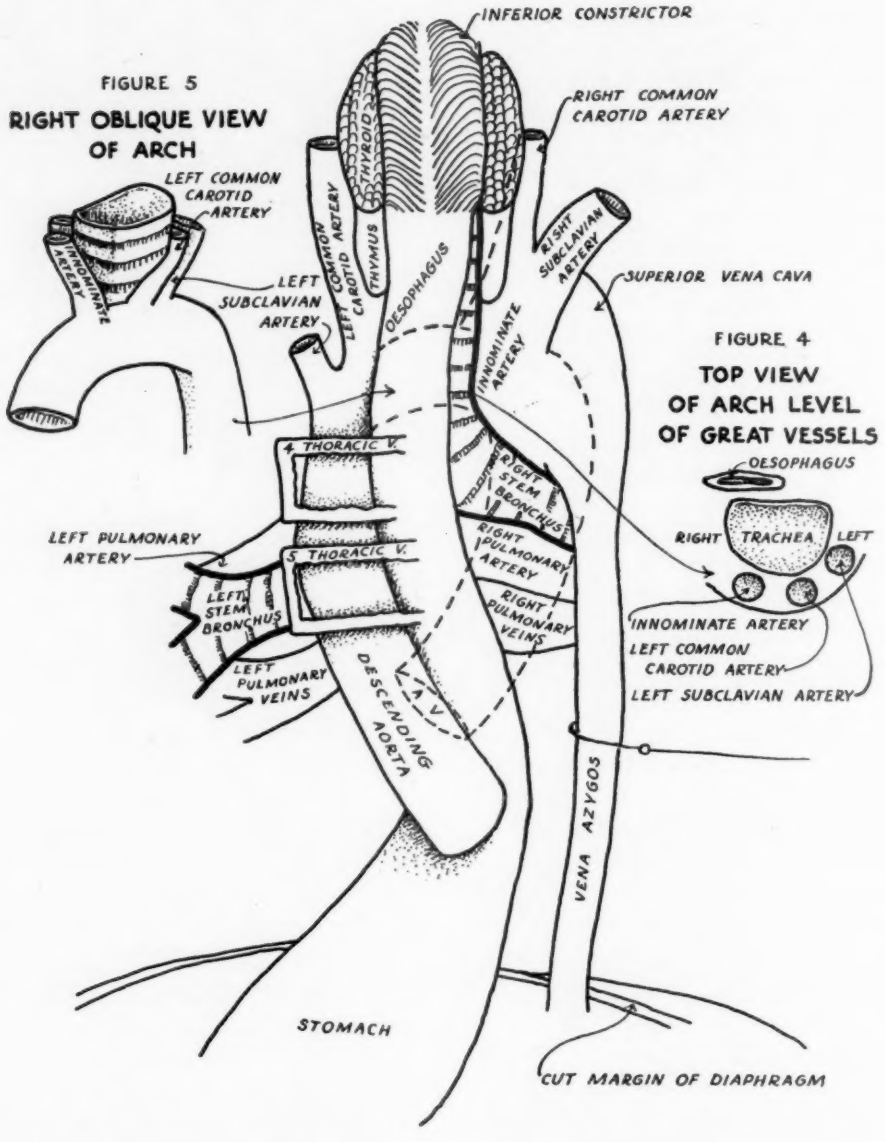


FIGURE 5

RIGHT OBLIQUE VIEW OF ARCH

FIGURE 4

TOP VIEW OF ARCH LEVEL OF GREAT VESSELS

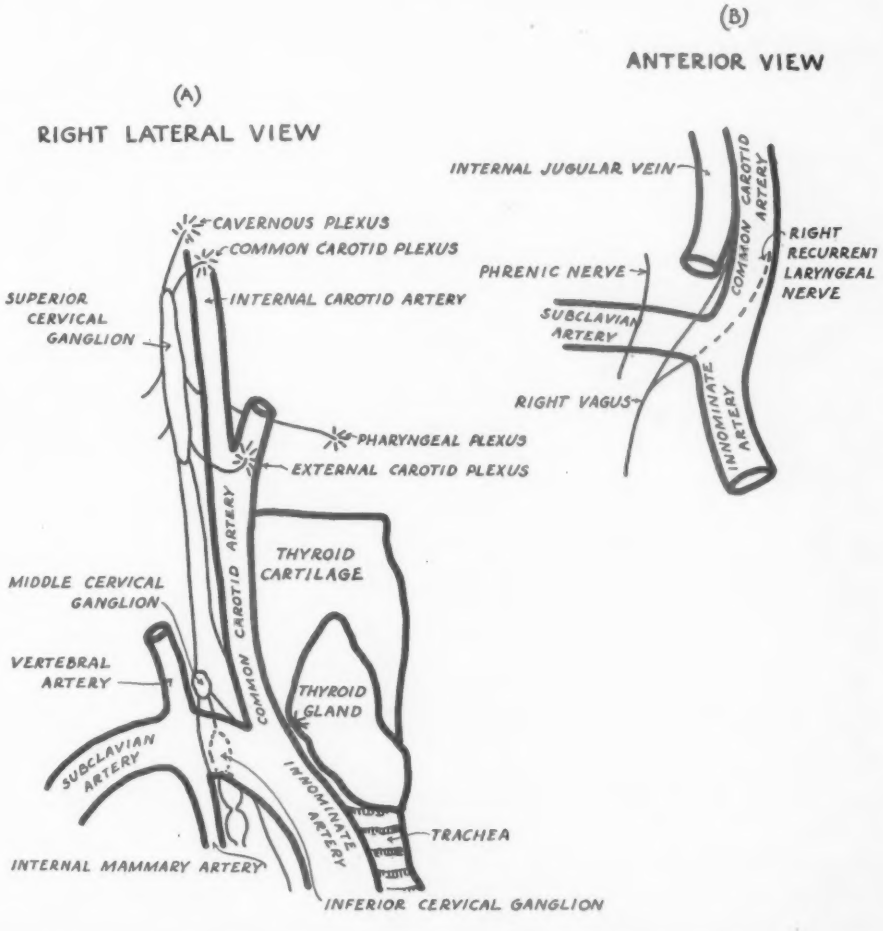
posterior view of the ascending aorta, the aortic arch, and the descending aorta. Broken-dash lines indicate the positions of the aortic valves, the aorta, and the great vessels lying in front of the trachea, the esophagus, and other organs. The vena azygos passing over the right bronchus is drawn aside by a hook. The components of the right and left lung roots are depicted, the ascending aorta passing in front of the right root structures, and the terminal arch coursing behind the left root structures, respectively. The left halves of the bodies of the fourth and fifth vertebrae are fenestrated to show the terminal arch lying anteriorly.

The arch of the aorta lies in the superior mediastinum and is posterior to the lower part of the manubrium sterni. It commences at a point posterior to the right

border of the sternum, at the level of the second costal cartilage, and extends to the level of the lower border of the left side of the fifth thoracic vertebra. It has two curves, one with the concavity downward, and, what is more important clinically, a concavity posterior and to the left (Figs. 1 and 3). Anteriorly, it is related to the (Fig. 1). Above, are the branches of the great vessels, whose origins are crossed by the left innominate vein (Fig. 1). Below, is the bifurcation of the pulmonary artery, the root of the left lung, the ligamentum arteriosum, and the left recurrent laryngeal nerve, lying between the aorta and the left pulmonary artery (Figs. 1 and 3).

FIGURE 6

INNOMINATE ARTERY AND RELATIONS



mediastinal pleurae, the lungs, and the remains of the thymus gland. On the left side, it is crossed by the phrenic and the vagus nerves, and the recurrent laryngeal branch passes under the concave border just outside of the ligamentum arteriosum (Fig. 1). Posteriorly, and to the right, are the trachea, the left recurrent laryngeal nerve and the left border of the esophagus

The Terminal Arch. It is recalled that the terminal arch is extended to the part of the aorta lying in front of the left half of the fifth thoracic vertebral body, so that this terminal portion of the arch has in front the left stem bronchus and behind the fifth vertebral body. Immediately preceding this, the aorta passes over the top of the root of the left lung, and behind it

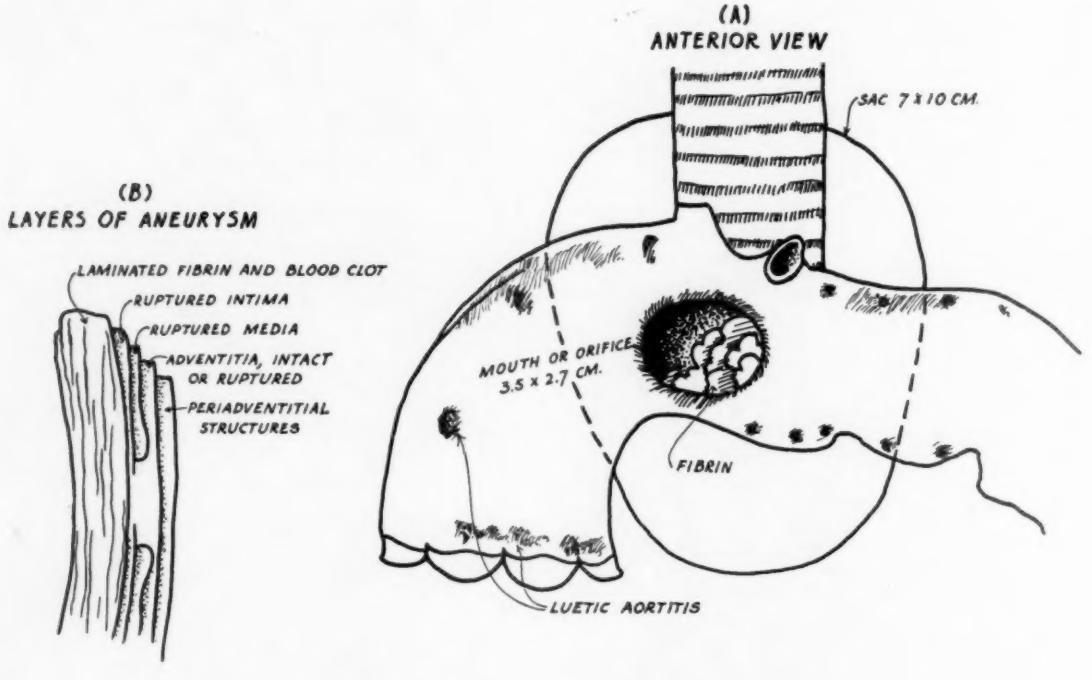
is the left half of the fourth vertebral body. This terminal arch therefore practically embraces the left bronchus and is in relation to the left border of the esophagus, which lies anteriorly (Figs. 2 and 3).

In general, the transverse arch has a posterior concavity whose termination at the origin of the left subclavian artery is at a level or plane posterior to that of its commencement, just proximal to the origin of the innominate artery (Fig. 4). This concavity closely hugs the anterior and the left lateral trachea above the tracheal bifurcation (Fig. 4). The termination of the aortic arch is in intimate relation to the left stem bronchus, the left border of the esophagus, the left half of the bodies of the fourth and fifth thoracic vertebrae, and the left recurrent laryngeal nerve.

Innominate Artery (Figs. 1, 5 and 6). The innominate artery extends from the posterior middle of the manubrium sterni to end near the right sternoclavicular joint. It runs upwards and posterolaterally in the superior mediastinum. Its relations are as follows: posteriorly, it is in contact with the trachea; anteriorly, the left innominate vein courses in front of the origin of the artery; right laterally, it is in contact with the right innominate vein, the upper part of the superior vena cava, and the right phrenic nerve; left laterally, at the lower level, is the left common carotid artery; at a higher level, the trachea is in contact with it (Fig. 5). Posteriorly, at some distance (Fig. 6 *A* and *B*) it is in relation to the inferior cervical ganglion and the cervical sympathetic trunk. At its termination is the right recurrent laryngeal nerve.

FIGURE 7

ANEURYSM OF THE TRANSVERSE ARCH



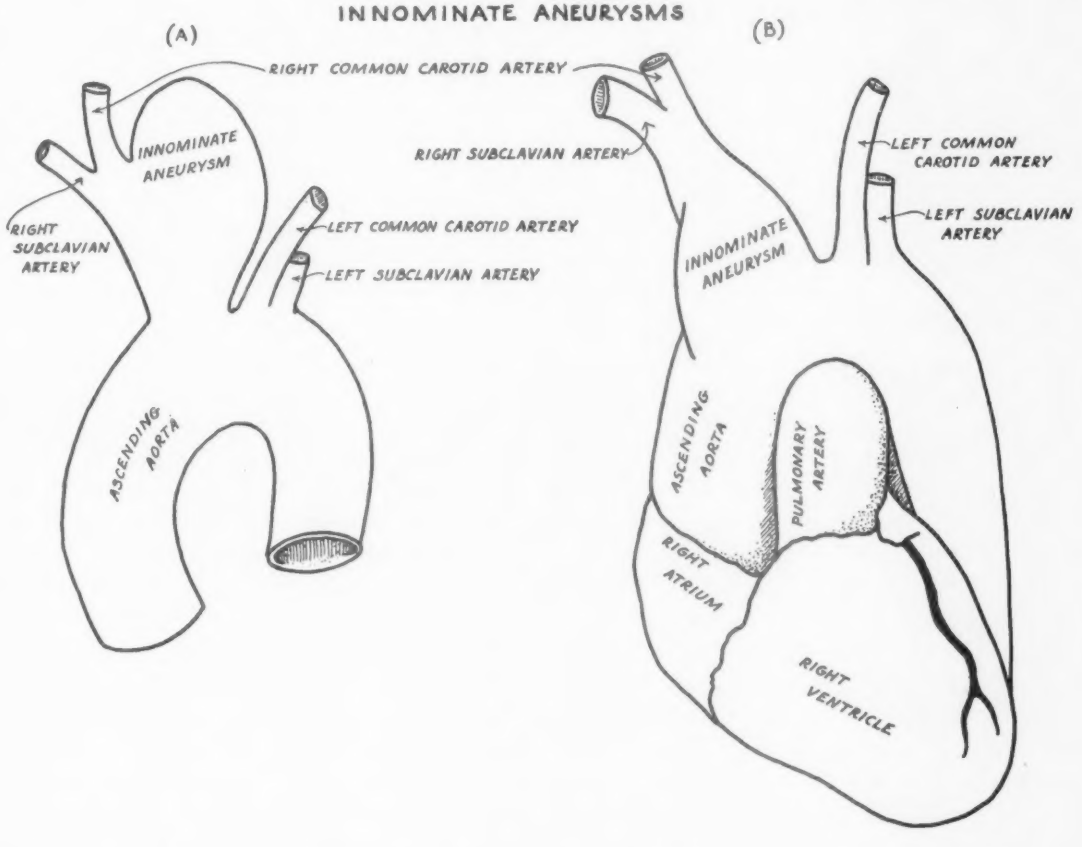
Clinical Pathology. The luetic process produces a weakening of a diffuse segment of the aortic walls, resulting in aneurysmal

dilatations of two types: (*a*) Fusiform, which is produced by a diffuse luetic infiltration with thinning of the walls and intact arterial layers. It is infrequent in occurrence and runs a benign course without pressure phenomena. (*b*) Saccular (Fig. 7 *A* and *B*), which is a luetic infiltration with thinning of a discrete portion of the aorta. This type may remain benign until rupture of the aortic wall takes place. Then, if situated near an important viscus such as the left bronchus, early pressure symptoms occur. Later there is more or less extension of the aneurysmal sac, the outer layer of which may be adventitial or periadventitial tissue. There are then produced adhesions to, and displacement of, important structures, fistulous openings into hollow viscera, and sudden large hemorrhages.

In the ascending aorta and arch, saccular aneurysms occur more frequently at the convex and posterior surfaces, because these parts are subject to greater hydrostatic strain from the moving column of blood.

Figure 7*A* is a schematic diagram of an aneurysm of the transverse arch, saccular type, with ruptured walls. The mouth measures 3.5×2.7 cm., and the sac 7×10 cm. A cross section of the wall (Fig. 7*B*) shows, from within outwards, laminated fibrin and a blood clot, ruptured intima, ruptured media, intact or ruptured adventitia, and periadventitial structures. Dynamic pressure and displacement of structures, adhesions or fistulae to neighboring organs, depend on local anatomical relations and the extent of the aneurysmal sac. Figure 9, *A* and *B*, illustrates a frequent, important finding in aneurysms of the terminal arch; namely, an irregular erosion

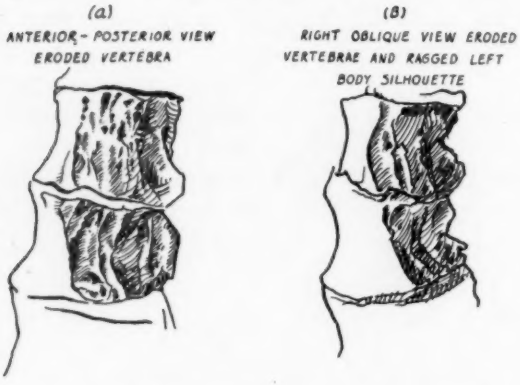
FIGURE 8



and osteosclerosis of the left halves of the bodies of the fourth and fifth thoracic vertebrae. It is necessary to note that the erosion is best shown in silhouette in the right oblique position (Fig. 9*B*).

Figure 8, *A* and *B*, shows the two common types of innominate aneurysms of the distal and proximal portions. Infrequently the entire vessel or the median portion is

FIGURE 9
EROSION OF
FOURTH AND FIFTH THORACIC VERTEBRAE



involved. There are early pressure phenomena because of the small caliber of the superior mediastinum and of the important neighboring organs (Fig. 6 *A* and *B*).

Clinical Aspects. Detailed studies of the physical signs and symptoms produced by aneurysms of various portions of the aorta have appeared in the literature from time to time.[2,3,4,5] We do not intend to explore all the possible signs and symptoms but rather to emphasize the anatomical relations of the aorta, and a knowledge of these relations, as shown in the accompanying illustrations, will serve to clarify and simplify the subject. Like all mass lesions in the chest, aneurysms give rise to what may be called general symptoms, more or less common to all types, and to symptoms tending to indicate the site of the lesion. Among the former, pain, cough, and dyspnea, are the most frequent. The special symptoms are peculiar to certain locations and result from pressure on certain vessels, nerves, or portions of the bronchial tree or esophagus.

It is well to remember that pain may result from pressure upon any structure within the thorax or upon the chest wall and, in the latter case, may be localized or may be segmental in distribution. Often, the pain is referred to both shoulders, both arms, the neck, the head, and the precordial area; but rarely to the back except when the terminal transverse arch or descending aorta is involved. Pain is possibly more frequent in the ascending group of aneurysms, but is common to all.

Pressure pain is usually associated with bone erosion and indicates that the aneurysm has reached the chest wall. Erosion of the ribs and sternum is usually less painful than erosion of the vertebrae but it should be emphasized that extensive erosion may occur without producing pain.

Cough is common to at least half of the group under consideration and is a manifestation of pressure upon the respiratory tract, causing irritation and deficient drainage. Any portion of the trachea, bronchi or lung, if irritated, produces a cough, with or without sputum. Hoarseness and a brassy cough occur in only a minority of cases and usually indicate transverse arch involvement, although the right laryngeal nerve may be irritated by an ascending arch aneurysm.

Dyspnea ranks high as an early symptom and may vary from a mild substernal oppression to the severe types, which resemble heart failure or asthma. Dyspnea is nearly always due to compression of the trachea, bronchi or lung. Dysphagia occurs in the transverse arch group, because here the esophagus may be intimately related to the lesion.

The physical signs and pressure phenomena which may be produced by aneurysmal sacs are numerous and often complex. Reference to the structures which may be pressed upon and to their anatomical relations will help to clarify the situation. Pointing of the aneurysmal sac may cause localized bulging and pulsations in the right or left upper chest, above the manubrium, above the clavicle, or in the

lower chest and back. Thrills and diastolic shocks are most numerous in the ascending and transverse arch groups, because of their anatomical accessibility. Cyanosis may occur in the ascending group from pressure on the superior vena cava, the pulmonary artery or the right auricle. Pressure upon the superior cervical sympathetic chain is probably responsible for the pupillary changes. The blood pressure and pulse inequalities in the arms result from direct pressure upon the vessels leaving the arch, from loss of pressure in the vessels arising directly from the sac or from loss of pressure in the sac itself. Because of anatomical requirements for production, tracheal tug is found in less than half the cases. It may occur in both the ascending and transverse groups; in fact, any condition which anchors the left bronchus to the aorta may produce it. The heart is usually normal in size unless the aneurysm is complicated by a luetic aortic insufficiency or by hypertension. Humming murmurs may occur over the sac, but are uncommon, and are not an important finding. Pressure upon the trachea or bronchi produces lung findings such as lagging of respiration, bronchiectasis or even evidence of infection in the lower lobes. Heart failure is not a part of the picture in aneurysms unless complicated by aortic insufficiency or other conditions affecting the heart. For those who are interested in a detailed analysis of symptoms and signs resulting from various types of aneurysms, reference should be made to the excellent presentation of Kampmeier.[5]

An aneurysm of the innominate artery usually presents a more definite clinical course and picture than does an aneurysm of the aorta, and obviously much is known[6,7] about this variety because of its tendency to present in the neck. Reference to its anatomical relations, as shown in Figure 6, will clarify the physical signs and symptoms. Pain in the right shoulder, cough, and the presence of a pulsating tumor above the episternal notch, have been the most common findings in our cases. This aneurysm tends to spread upward beneath the sternomastoid muscle and to compress and erode the sternum and clavicle; yet, having more space in which to spread, its symptoms usually become manifest later than do those of an aneurysm of the arch. In those cases where the arch of the aorta and the innominate are both involved, the tumor displaces the aorta, heart and trachea downward and to the left. In this type of aneurysm, there may occur venous congestion of the face (uncommon in our experience); cough, aphonia, and hoarseness from pressure on the right recurrent laryngeal nerve; changes in the pupils because of pressure on the sympathetic chain; pain referred to the arm, shoulder, head, or neck, from brachial or cervical plexus pressure; and dyspnea, as well as dysphagia, because of tracheal and esophageal pressure. Cough, dyspnea, and pain were by far the most common complaints.

ROENTGENOLOGICAL DIAGNOSIS

Obviously, this is the most important part of the examination, since size and location are thus accurately determined. In our experience, many aneurysms were first demonstrated by the roentgen ray, and changes in the lungs and related structures which clinically had been thought to be primary were thus shown to be secondary in nature. The aneurysms are usually much more dense than any of the surrounding structures, and the majority present smooth, rounded borders. Pulsations may be seen; but, in our experience, differentiation between expansile pulsations and motion transmitted from the heart has been impossible except in isolated instances. In fact, the great majority of aneurysms do not pulsate, because of disease in the wall, calcification, or the presence of a mural clot. All cases should be roentgenoscoped, since only in this way can a mass suggesting an aneurysm be separated from the great vessels, and the differentiation between a tumor and an aneurysm correctly made. In roentgenoscopic studies, pulsa-

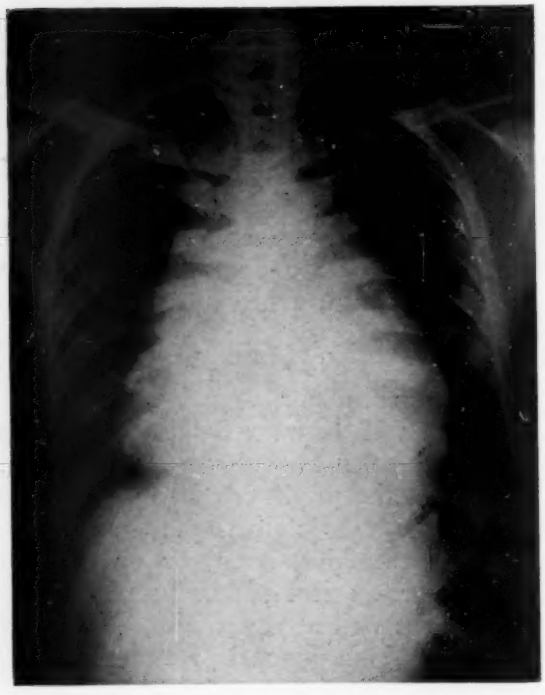


FIG. 10. Large fusiform aneurysm covering the entire heart shadow, no encroachment on the neighboring structures. The heart shadow is visualized through the fusiform aneurysm.

tions are best seen in the fusiform type (Fig. 10), in which there is usually an absence of blood clot and laminated fibrin. The pulsations are expansile in type, with a rapid expansion and a quick rebound of the aortic shadow. In the saccular type, it is only in the early stages that we see expansile pulsations. After the formation of clots and laminated fibrin, fixation of the sac to the surrounding structures usually abolishes all expansile pulsations, and only transmitted movement is seen. Roentgenographic studies in the posteroanterior, lateral, and both oblique views offer the best means of clearly outlining the sac. The heart in the great majority of aneurysms of the aorta is not enlarged, and where enlargement occurs there is usually an aneurysm in the sinus portion of the aorta, causing aortic insufficiency. Syphilis of the aortic valve may be present in conjunction with an aneurysm higher along the arch. There is no physiological reason why a simple aneurysmal dilatation of the aorta should cause increased work for the heart. Very small saccular aneurysms are difficult to detect anywhere. Those in the heart mass, and smaller ones arising from the mid-portion of the convex and concave portions of the aortic arch, are particularly hard to detect. However, a careful study of the trachea, the esophagus, the bifurcation, and the right and left main stem bronchi, is often helpful in detecting an aneurysm even in these locations, either because of encroachment on the lumen of the trachea and the bronchi or because of compression or displacement of these structures. Fusiform aneurysms produce sharp oval or semicircular out-pouchings, well circumscribed and often delineated by atheromatous plaques, which extend into either the right or left lung field and may overshadow, but not obliterate, the right or left cardiac border. Saccular aneurysms produce sharply circumscribed oval or semicircular shadows, continuous with the heart border and often delineated by thin, dotted, calcified plaques just inside the outer border of the sac. They produce characteristic erosion in the anterior and the lateral surfaces of the bodies of the vertebrae (Fig. 9). Because the intervertebral discs resist the destructive process better than the bodies of the vertebrae, the portions of the bodies nearer the discs are very little involved, producing scaphoid erosion of the bodies with intact overhanging edges.

Aneurysms of the Ascending Aorta (Fig. 11). Saccular aneurysms of the ascending aorta, from the vasoatrial junction to the beginning of the horizontal arch, extend most often into the right lung field, obliterating the right cardiac borders and, if large enough, may displace the heart and the aorta to the left. They may also extend anteriorly, and here the sternum and the chondral portions of the anterior ribs may be eroded (Fig. 12). The lower portions of the trachea and the main bronchi are very seldom encroached upon unless the aneurysm is large enough to extend well backward, and then the lower portions

of the trachea and the main bronchi are displaced backward. Aneurysms with small pedicles attached to the ascending aorta are not uncommon and may resemble lung tumors.

Aneurysms of the Aortic Arch and Innominate Artery. Here, besides the characteristic oval, circular, or semicircular shadow, continuous with the heart border, we have other important criteria. We might say that generally all aneurysms of the arch displace the trachea to the right except the innominate and those arising from the extreme anterior portion of the horizontal arch, in which the trachea, if the aneurysm is large enough, is displaced to the left. Those arising from the anterior two-thirds of the arch displace the trachea backward (Figs. 13 and 14), as does also the innominate aneurysm; and those arising from the distal horizontal and descending aorta displace the trachea anteriorly. The esophagus, being a more posterior structure, is displaced to the right and anteriorly

Fig. 11. Saccular aneurysm of the ascending aorta extending into the right lung field, obliterating the right cardiac border. Heart enlarged due to associated aortic insufficiency.

Fig. 12. Large saccular aneurysm destroying the manubrium, and anterior portion of the right first rib, protruding anteriorly beneath the skin, with subsequent rupture.

by aneurysms in the descending and distal portions of the arch. In other types, the aneurysm, if large enough, displaces the esophagus backward and to the left. The most common of all aneurysms we have encountered is the one arising from the distal, horizontal, and descending portions (Figs. 15 and 16). Here, in the posteroanterior view, the trachea and, to a lesser extent, the esophagus are displaced to the right; the left main bronchus is pushed downward and inward; and the lumen is narrowed. At times enough pressure is exerted on the lumen to produce atelectasis of the left lower lobe, and occasionally of the entire left lung, followed by infection and pleural effusion. When atelectasis or effusion occurs on the left side, the aneurysmal sac is entirely obscured and no indication of it will be seen on the roentgenogram (Figs. 17 and 18). However, in spite of the effusion and the atelectasis, which may cause a retraction of the heart to the left, the trachea is usually displaced

FIG. 13. Large saccular aneurysm with calcification of the sac, arising from the anterior two-thirds of the horizontal arch displacing the trachea to the right.

FIG. 14. Lateral view of Figure 13, showing the calcified aneurysm displacing the trachea backward and producing early erosion of the fourth and fifth dorsal vertebrae.

to the right in an arc-like fashion. A diagnostic pneumothorax, or removal of fluid with replacement by air, is a very important diagnostic measure. This type of aneurysm produces the typical anterior and lateral erosions of the dorsal vertebrae, previously described. We have observed several cases where the entire left half of the bodies of the fourth, fifth, and sixth dorsal vertebrae have been destroyed

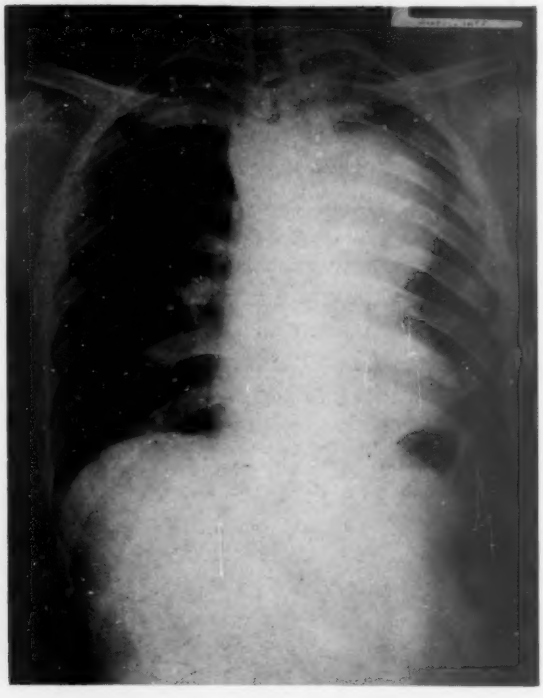


FIG. 15. Saccular aneurysm arising from the distal, horizontal and descending aorta, displacing the trachea and esophagus to the right. Heart not enlarged.

by the aneurysm (Fig. 19). To differentiate an aneurysm of the distal, horizontal, and descending aorta from diffuse dilatation, we must remember that in a true saccular aneurysm, because of the presence of laminated clots and fibrin, the density is greater than that of the heart mass, and the heart and the remainder of the aorta cannot be visualized through the aneurysm in the posteroanterior view. In the lateral view, the aortic knob is replaced by the sac. In the left anterior oblique, the sac is seen to encroach on the posterior portion of the

aortic window, and the trachea, as well as the esophagus, is narrowed and displaced to the right and anteriorly.

An aneurysm arising from the proximal portion of the innominate artery will produce a widening of the superior mediastinum (Fig. 20). The outer border is usually well-defined and straight, though sometimes oval in outline. It extends upward and to the right and fades into the neck

Fig. 16. Lateral view showing erosion of the fourth, fifth and sixth dorsal vertebrae, and anterior displacement of the trachea and esophagus by aneurysm arising from the distal, transverse and descending aorta.

tissue shadow. The inner border is usually obscured by the shadows of the spine and the mediastinum; but, when the sac is large enough, may be seen just to the left of these. When both borders are well visualized, the sac is shaped like a vase. The aortic knob is displaced downward and to the left; the trachea and the esophagus are displaced to the left and posteriorly; and the inner portion of the right clavicle, the manubrium, and the chondral portion of

Fig. 17. Aneurysm of the distal, transverse and descending aorta with pressure on the left main bronchus and azygos veins, with atelectasis and effusion in the left lung.

Fig. 18. After removal of fluid and introduction of air the large sac is visualized as well as the atelectatic left lung.

FIG. 19. Extensive destruction of the left half of the body of the fourth, fifth and sixth dorsal vertebrae and the approximating posterior ends of the fourth, fifth, sixth and seventh ribs.

the right first rib may be eroded. When the sacs are small, there is usually no involvement of the neighboring structures; when large, the right wall of the trachea is first encroached upon, the lumen narrowed and somewhat compressed, and the lower portion displaced to the left and somewhat tapered. An aneurysm in the extreme anterior portion of the arch will displace the trachea and esophagus in much the same manner as the innominate type, but an aneurysm in this region practically always involves the innominate artery.

Small aneurysms between the tracheocephalic vessels in the mid-portion of the arch may not encroach on the trachea or the esophagus. Aneurysms arising from the concave portion of the arch are more difficult to diagnose and visualize; but here, also, attention must be given to the lower portion of the trachea and its bifurcation, as well as to the right and left main bronchi. Aneurysms arising from the anterior portion of the concave arch will displace these structures posteriorly; and, conversely, those arising from the posterior portion of the concave arch will displace them anteriorly.

The differential diagnosis of mediastinal and lung tumors is at times difficult. An innominate aneurysm may resemble a tumor in the superior mediastinum, particularly a substernal thyroid. The latter, however, moves upon respiration, swallowing, or grunting, and the aortic arch is distinctly separated from it. An enlarged right lobe of the thyroid produces an arch-like displacement of the trachea, with narrowing of the lumen, most marked in the region of the middle superior mediastinum. The left lobe of the thyroid displaces the trachea to the right. The lymphoblastoma group of tumors, such as Hodgkin's disease, lymphosarcoma, leukemia and thymoma, are usually situated in the anterior mediastinum, and the trachea is very seldom displaced laterally. If the tumor is large

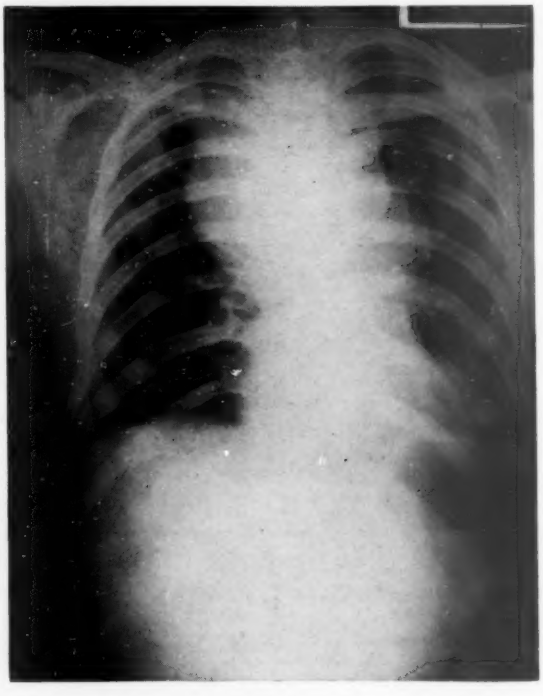


FIG. 20. Saccular aneurysm of the innominate, displacing the aortic knob downward and to the left and the trachea to the left and backward. The borders are sharply outlined, extending upward into the superior mediastinum.

enough, there may be a posterior displacement of the trachea. The aortic arch (with adequate films) can usually be separated from the mediastinal mass. These tumor masses are bilateral, enlarged in the vertical diameter, have indistinct outlines, and rarely show calcification. Mediastinal neurinomas may resemble an aneurysm, as they are usually fairly well outlined, unilateral, and may be dense enough to obscure the aortic arch. However, they affect the spine differently, produce a widening of the foramina and irregular erosion of the lateral portion of the bodies and the pedicles. At times, bronchogenic carcinoma may show a tumor mass not unlike an aneurysm. However, there is often some atelectasis, malignant lymphangitis, or tumor masses in the lung fields and, often, metastatic glands in the hilar and mediastinal regions. Loculated tuberculous pericarditis or other types of pericarditis may resemble aneurysms, but the size of the heart, absence of pulsations, clear lung fields, and other signs of pericarditis are usually present.

Prominence of the pulmonic salient as seen in pulmonary stenosis, interatrial septal defects, and patent ductus arteriosus, may also suggest an aneurysm. However, the markedly increased pulsations, as well as prominent and pulsating hilar vessels, together with right heart enlargement, usually make a differentiation possible. Aneurysmal dilatation of the left atrium, where the left atrium extends well over to the right, overriding the right atrial border, bears some resemblance to an aneurysm, but here the cardiac configuration is that of mitral stenosis and the lung fields show distention of the hilar and the perihilar vessels. Occasionally Pott's disease, with a mediastinal abscess, produces a bilateral mediastinal tumor resembling an aneurysm, but a careful study of the spine and the aortic arch will easily differentiate it from an aneurysm.

CONCLUSION

Many articles dealing with aneurysms have been published but only a very limited number have been accompanied by anatomical studies. We have attempted in this presentation to emphasize the anatomical relation of the aorta and to show how a knowledge of this, as detailed in the accompanying illustrations, may serve to clarify and simplify the subject. Not only will this detailed anatomical relation be valuable in the diagnosis of aneurysms but it will also greatly aid in a differential diagnosis of all space-taking lesions which occur in the thorax, adjacent to the aorta.

We wish to express our appreciation of the cooperation and assistance of Dr. B. Robinson who has drawn the illustrations from his extensive autopsy studies.

REFERENCES

1. Ostrum, H. W., Robinson, B. D., Nichols, C. F., and Widmann, B. P. Aneurysms of aortic sinuses or sinus of Valsalva. Am. J. Roentgenol. & Rad. Therapy, 1938, *40*, 828–837.
2. Hare, H. A., and Holder, C. H. Some facts in regard to aneurysm of the aorta. *Am. J. M. Sc.*, 1899, *118*, 399.
3. Boyd, L. J. Study of four thousand reported cases of aneurysm of thoracic aorta. *Am. J. M. Sc.*, 1924, *168*, 654–668.
4. Lucke, B., and Rea, M. H. Studies on aneurysm. I. General statistical data on aneurysm. *J. Am. M. Ass.*, 1921, *77*, 935.
5. Kampmeier, R. H. Saccular aneurysm of thoracic aorta; clinical study of 633 cases. *Ann. Int. Med.*, 1938, *12*, 624–651.
6. Warfield, C. H. Roentgen diagnosis of aneurysms of innominate artery. Am. J. Roentgenol. & Rad. Therapy, 1935, *33*, 350–358.
7. Parks, H. Aneurysm of innominate artery. *Arch. Int. Med.*, 1938, *61*, 898–909.

THE ROENTGENOLOGICAL DEMONSTRATION OF THE TRUE ARTICULAR SPACE

WITH PARTICULAR REFERENCE TO THE KNEE JOINT AND THE INTERNAL SEMILUNAR CARTILAGE*

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THE true articular space like the pleural space is a potential space which is visualized only under special conditions. A layer of articular cartilage covers the end of each bone at a diarthrodial joint and the two layers are ordinarily in close approximation to each other separated only by a thin layer of fluid. These two cartilages are normally represented by a uniformly radiolucent space between the bones, and changes in the cartilage are commonly implied from variations in the width of this space. An increased space is taken to indicate swelling and edema of the cartilage as the result of injury or disease or to a separation of the cartilages from an increased amount of articular fluid, a loose body locked between the cartilages, or relaxation of the capsular ligaments. Narrowing of the space indicates degeneration or destruction of the cartilage and rarely there may also be calcification. These implications without more direct evidence generally suffice. The knee, however, offers a special case for there are not only the cartilaginous coverings of the tibia and femur, but also the two semilunar cartilages which are subject to injury and disease and which then may become a basis for serious disability. The clinical diagnosis of meniscus injuries is often difficult and inaccurate at best. Schaer,[1] in a recent study, estimates the incidence of positive and negative errors in diagnosis in his clinic as 15 per cent and the diagnosis becomes, of course, more difficult and important in medicolegal and compensation cases. In recent injuries the roentgen examination has been chiefly of value in excluding involvement of the bone structure, although there may be evidence of effusion into the joint and perhaps an increase in the spacing at the site of the lesion. In old cases there may be demineralization of the bone structure about the affected knee with either an increase or decrease of the spacing between the tibia and femur on the side of the cartilage injury. Frequently we have also noted a localized sclerosis of the tibial tuberosity just beneath the affected semilunar cartilage when comparison is made with the sound knee. These changes, however, are all indirect ones and there is a real need for direct visualization of the deformity of the semilunar cartilage. Sporadic attempts at endoscopy or the injection of opaque media, e.g., air or uroselectan, which have been carried out for many years have apparently not been of such consistent value as to justify the operative procedures involved and warrant more general use.

In 1932 Dittmar[2] published his observations in demonstrating the true articular space at the medial aspect of the knee in two patients by forcible abduction. He believed this was possible only in children or in adults where there was weakness of the collateral ligament. Felsenreich[3] in 1935 reported observations on two patients showing subluxation of the medial meniscus, but said the procedure was rarely of value in demonstrating the semilunar cartilage, although it might be useful in testing the integrity of the collateral ligaments. A more complete study of the method was made by Nordheim[4] in 1938. His observations in this paper were confined to normal individuals. He was able to show that forcible abduction or traction separates the articular cartilages, leaving a relative vacuum between them which provides contrast for the shadows of the cartilage. After a number of minutes of continued traction this vacuum is replaced by fluid withdrawn from the tissues. The converse of this ob-

* Read at the Third Annual Clinical Conference of Mid-Western Radiologists, Detroit, Mich., Feb. 10–11, 1939.

servation is also true, i.e., the space can only be demonstrated when there is a negligible quantity of fluid within the joint. The joint space together with the internal semilunar cartilage was demonstrable in about 70 per cent of normal knees, while the external space was shown in only 2 of 30 attempts. Nordheim was also able to show

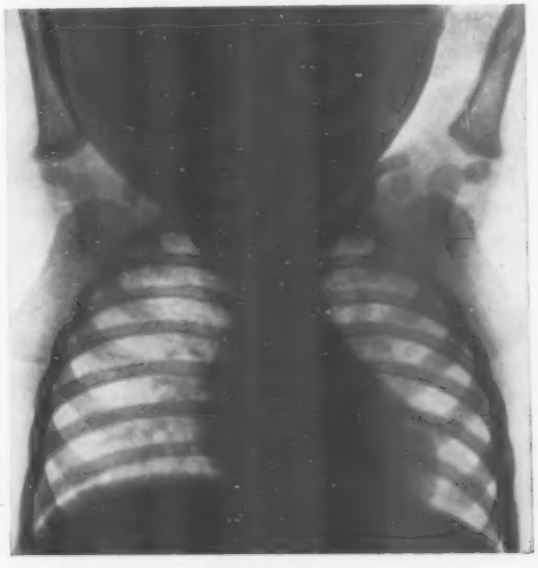

Fig. 1. A routine film of a child's chest showing the space between the articular cartilages at the shoulder joints produced by traction on the arms.

the true articular space by forcible traction at the phalangeal and shoulder joints.

For the past few months we have made observations with the method and believe that the results warrant consideration and further investigation. Occasionally the true articular space is visualized inadvertently as, for example, in children undergoing a chest examination with the arms raised and held close to the head (Fig. 1). Very often sufficient force is exerted to separate the cartilages at the shoulder joint and the space is revealed as a fine crescent shaped line. We have also seen the space at the hip joint when the child was forcibly restrained (Fig. 2). Rarely the true joint spacing is seen at the knee in the routine examination. Hippe and Hähle,[5] in reviewing a large number of films, reported observing the space in 25 knees with arthronosos deformans, and in 5 apparently normal. Löhr and Hellpap[6] studied 642 films of the knee and observed the spacing only twice, once in a normal

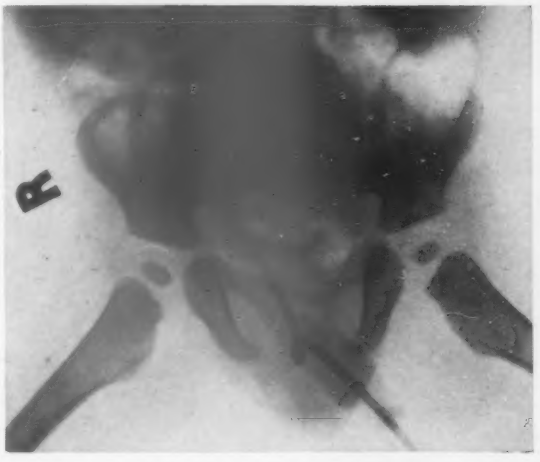

Fig. 2. The true articular space shown at the right hip joint in a child forcibly restrained.

Fig. 3. The articular space at the medial aspect of the knee shown in a routine examination of a patient having osteo-arthritic changes and degeneration of the cartilage.

knee and in one with extensive degenerative changes. We have recently seen the space in a knee examined in the usual manner (Fig. 3). This patient was sixty-two years old and a retired police inspector who was working as a watchman. He had complained of weakness and pain in both knees for twelve years. Roentgen studies revealed well marked degenerative osteo-arthritic changes demonstrable on both sides. At the medial aspect of the right knee was a dark linear shadow which we interpreted as the space between the articular cartilages. The mechanism of its production is not clear, but it has been observed to occur most often when there is degeneration of the cartilage, as in this case.

FIGS. 4 and 5. The semilunar cartilage and the articular cartilages of the tibia and femur together with spacing between them shown by forced abduction in two normal knees.

The technique which we have employed for the demonstration of the internal meniscus is very simple and requires no special apparatus. With the patient lying on his back and a small screen cassette under the knee, a cylindrical cone measuring about 25 cm. in length and a 8 cm. in diameter and well padded at both ends is placed with one end against the external aspect of the knee joint and the other end against the chest of the examiner. Strong traction is then made by the examiner with the hands on the thigh and lower leg. This is maintained for a period of five seconds to the limit of the examiner's strength or to the sensation of pain for the patient, when the exposure is made with the ray projected in a direction parallel to the upper surface of the tibia. This is best accomplished with very slight flexion at the knee. Only very rarely does the procedure cause the patient even temporary discomfort. We have found this method more fruitful than a mechanical screw device for exerting pressure. If the pressure is too long maintained Nordheim has shown that fluid is withdrawn from the tissues and the space is obliterated. The manual method permits a more careful regulation of the tension and also a small increment of tension may be applied at the instant of exposure.

The meniscus appears on the film as a long triangle with the base attached to the internal collateral ligament and the tip directed toward the tibial spines. The cartilaginous coverings of the tibia and femur are also shown. Our experience is in agreement with that of Nordheim who was able to show the cartilage in about 70 per cent of normal individuals. Figures 4 and 5 illustrate the findings in two normal young adults of each sex. Occasionally a mottled appearance at the joint is obtained (Fig. 6). This we believe is probably due to a droplet-like formation of the articular fluid as suggested by Nordheim. It is more difficult to show the external semilunar cartilage, but we were able to obtain a faint delineation of this structure in two children (Fig. 7). Fortunately it is not so important to demonstrate this meniscus as it is much more rarely subject to injury than the internal semilunar cartilage.

Fig. 6. A slight variation in the appearance of the spacing of a normal knee. The mottled appearance is probably due to the behavior of the articular fluid.

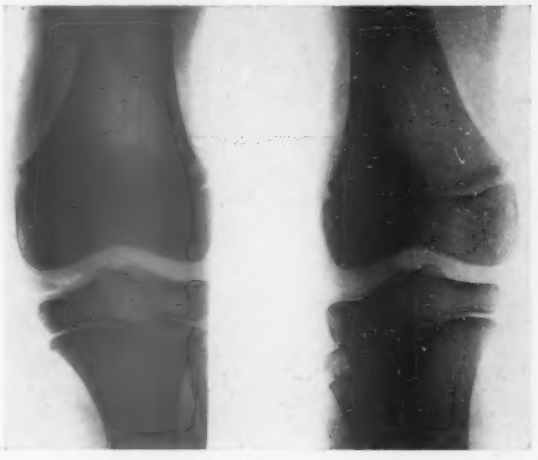

Fig. 7. Both internal and external articular spaces with the semilunar cartilages shown in a healthy child.

An injury to the internal semilunar cartilage results in pain and effusion. For both of these reasons this method is not applicable to the study of the acute injury. It is also not to be used in old cases when there is evidence of effusion into the joint as there can be no expectation of demonstrating the space by separation of the cartilaginous surfaces. In such instances Schaer has recommended aspiration of a small amount of the fluid for bacteriological, cytological, and chemical studies and its replacement with 4–5 cc. of uroselectan and an anesthetic solution followed by roentgen studies in various projections. The results of such examinations, however, have not often been helpful and may be misleading. Nordheim favors the injection of air when fluid is present with the examination made in various positions so as to bring the air into contact with the structures in question.

The method which we have described is then suited only to cases of old injury where no effusion is present and here valuable information may be obtained. In Figure 8 are shown the findings obtained in A. S. who sustained an injury to his left knee ten years previously when broad jumping and who has had recurrent difficulties since.

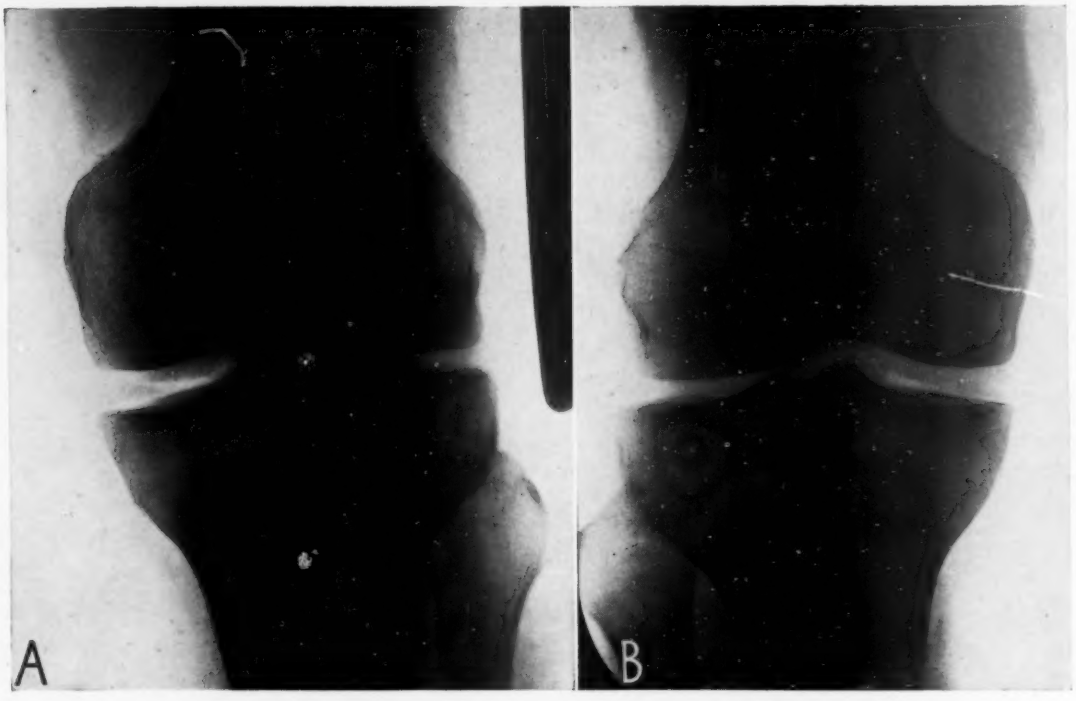

Fig. 8. The articular spacing in both knees of a subject who suffered an injury to his left knee ten years ago. *A*, the right knee presents a normal appearance while on the left, *B*, there is irregularity of the internal semilunar cartilage which represents the end-result of an old tear.

On the right side the semilunar cartilage presents a normal appearance while on the left there is a marked irregularity in the contour of this structure which we interpret as the result of an old tear.

It is not to be expected that this procedure will always or even usually yield conclusive results. In both the normal and abnormal case the semilunar cartilage may not be demonstrable. When it is demonstrated only gross abnormalities may be evident. According to Schaer important traumatic lesions may be present in the semilunar cartilage and warrant excision of the cartilage which are not evident to inspection at operation and which are revealed only by microscopic examination. Such lesions, of course, would not be revealed by this procedure. The procedure does give evidence of the integrity of the collateral ligaments which are of prime importance in the stability of the knee. On the affected side when there is weakness of the collateral ligament, forcible abduction will yield a greater space between the femur and tibia than on the normal side, as pointed out by Felsenreich. If, then, the uses and limitations of the method are understood, we believe this is an additional diagnostic procedure which will occasionally yield helpful information in the study of the knee joint.

References

1. Schaer, Hans. Der Meniskusschaden als klinisches, anatomisch-pathologisches und unfallmedizinisches Problem. Georg Thieme, Leipzig, 1938.
2. Dittmar, O. Der Kniegelenk-Meniskus im Röntgenbilde. *Röntgenpraxis*, 1932, *4*, 442–445.
3. Felsenreich, F. Darstellung des verletzten Meniscus medialis im Röntgenbild bei veralteter Kreuzband- und Seitenbandverletzung. *Röntgenpraxis*, 1935, *7*, 331–333.
4. Nordheim, Y. Eine neue Methode, den Gelenkknorpel, besonders die Kniegelenkmenisken, röntgenologisch darzustellen. IV. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1938, *57*, 479–495.
5. Hippe and Hähle. Quoted by Löhr and Hellpap, ref. 6.
6. Löhr, R., and Hellpap, W. Der Kniegelenkspalt im Röntgenbild. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1938, *58*, 45–56.

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OSTEOCHONDRITIS DISSECANS

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OSTEOCHONDRITIS dissecans, first described as a distinct pathologic entity and named by König in 1879, is a disease characterized by the separation, partial or complete, of a piece of articular cartilage, with or without part of the subjacent bone, from the ends of certain long bones.

Munro in 1758 was the first to recognize that loose bodies in joints originated from the articular surface.

Paget thought that these joint bodies were caused by "quiet necrosis."

König in 1879 and in a subsequent paper in 1887 was really the first to classify osteochondritis dissecans as a definite entity. His description was that "without any injury fragments separate from articular surfaces. The bony surfaces of the fragments become covered with dense connective tissue and cartilage. A similar change takes place within the defect from where the fragment originated. At the same time, there is slight effusion and villous hypertrophy."

INCIDENCE

This is not a rare condition and has often been reported. It is most common during adolescence and early adult life and occurs more frequently in males.

It has been described in a number of joints including the hip, ankle and metatarsal articulations, but the far greater number appear to occur in the knee or elbow. While there is a tendency toward the inclusion of osteochondritis dissecans in one group having presumably the same etiology, namely, Köhler's, Legg-Perthes', Freiberg's, Kienböck's, Osgood-Schlatter's, etc., there are some who believe this disease a distinctly separate entity with a specific etiology. The reasons advanced for this belief are: (1) the characteristic roentgenological and pathological appearance; (2) the circumstance that these changes occur not only almost exclusively in the knee or elbow, but in characteristic locations within these joints. In the knee, it is the lateral part of the internal condyle of the femur; in the elbow, the capitellum of the humerus.

ETIOLOGY

Several theories as to the etiology of the disease have been advanced which merit brief discussion. König, believing that the disease represented an inflammatory process, ascribed it to a low grade infection of unknown origin. Axhausen has suggested that the cause may be in small emboli of end arteries, resulting in infarction and a quiet, aseptic necrosis of the bone and cartilage deprived of its blood supply. Bernstein felt that the tendency to occur in families, and bilaterally in the individuals, suggests a constitutional abnormality, analogous to rickets, fragilitas ossium, coxa vara, etc. Phemister believes that the etiology may be similar to that of ununited fractures.

All investigators believe that trauma is predisposing. The trauma may represent direct violence, ligamentous pull or injury to arterial supply by long continued mild insults, as suggested by Sommer. Freiberg has further developed this viewpoint by the observation that in the knee the disease in its usual location is associated with a long tubercle of the medial tibial spine and that this may traumatize the involved area of the femoral condyle when the knee is in flexion and external rotation. Sommer and Fairbank have found a definite history of trauma in more than half of their cases.

Two other theories, that of fat embolism occluding the end arteries, and that regarding the process as a low grade arthritis or localized osteo-arthritis, have no supporting evidence.

PATHOLOGY

The pathology of the disease has been formulated largely from gross inspection of the knee at operation and from examination of the excised specimen; little is known of the picture in the remaining main body of the involved bone.

The disease process begins at the point of greatest contact in the knee joint—i.e., most frequently the medial aspect of the most prominent inferior surface of the medial condyle opposite the anterior tibial spine. Here a conical or discoid fragment of bone separates gradually from the underlying epiphyseal bone. The separation is gradual and may take months or years. Both the cavity and the separated side of the loose body become covered with fibrocartilage. Early in the process, the separating fragment may be held in place by a bridge of articular cartilage or synovia; or there may be at times only a fissure or circle of discoloration apparent in the articular cartilage, marking the limits of the underlying diseased plaque.

There are three stages then in which the loose body may be found:

(1) Retained in the original bone cavity. Under these circumstances, the articular surface is convex and covered by hyaline cartilage; the deep surface will be rough and covered by fibrocartilage.

(2) Loose in the joint. Here the bodies tend to become rounded and may grow by accretion of new bone. The hyaline layer is usually changed into fibrocartilage. The separated body may break up into a number of smaller fragments.

(3) Attached to synovial villi. Sometimes a free body may become attached to synovial villi and a pedicle forms, resulting in rapid proliferation and enlargement of bone and cartilage.

Microscopically the findings in the excised specimen are reported either as chronic inflammation or aseptic necrosis. The majority, however, have been unable to demonstrate inflammatory changes. In general, the degree of necrosis present varies inversely with the degree of attachment as classified above. The defect in the bone may remain as such, or may fill in gradually after complete separation has taken place.

CLINICAL FINDINGS

The history is usually of several years' duration. Complaints are of soreness, stiffness and occasionally swelling of the involved joint. Locking is common, especially in cases with a completely separated fragment, but at times in patients where separation is not complete. King has described 4 cases in which the onset was acute subsequent to a mild trauma and presenting painful, tender, swollen joints locked in 15–45° flexion. In all of these cases, two or three loose bodies in the joint were demonstrated, and there can be little doubt that the process antedated the trauma and was merely unmasked by it.

Objective signs are few: demonstration of one or more loose bodies in such cases as these are present; sometimes fluid; some limitation of motion and wasting of the quadriceps in chronic cases. Axhausen has described a sign where, with the knee flexed, pressure upon the lateral aspect of the medial femoral condyle (the usual site of involvement) elicits an acute local tenderness.

Finally, cases have been described which are completely asymptomatic, this usually occurring in patients in whom the contralateral knee was clinically involved, and the second knee roentgenographed as a control.

ROENTGEN FINDINGS

Since there is nothing characteristic in the clinical picture of the disease, the diagnosis has been made roentgenographically in the great majority of cases. The lesion is best seen in the anteroposterior roentgenogram and is apt to be overlooked entirely in the lateral view. It consists of a defect, usually shallow and sharply defined at the typical location described above, and usually circular in outline. The immediately adjacent bone shows a narrow zone of increased density; there may be atrophy of

the bones as a whole in chronic cases. This defect may contain a separated or hinged fragment of bone which most frequently is partially decalcified, or it may be entirely empty. Richards and Freiberg have described 2 cases in which only a line of separation was seen in the roentgenogram with no decalcification, and the surgical finding was merely a fragment of bone, completely separated but held in position by intact articular cartilage. At the other extreme come those cases, of which our Case 1 is an example, in which a definite defect in the subchondral bone is demonstrated roentgenographically, but in which, on operation, only a discoloration, loss of lustre and roughening of the cartilage is found. If the fragment of bone and cartilage is actually free in the joint space, it may be, although often is not, radiopaque, and only the defect corresponding to its earlier site will be seen. In those cases in which one or more joint mice are present and are not decalcified to the degree of becoming translucent to the roentgen ray, they tend to migrate to the regions of the joint where they will interfere least with motion, i.e., the subquadriceps bursa and the posterolateral pouches. King has stressed the necessity for differentiating free bodies in the latter location from the sesamoid bones commonly found in the gastrocnemius tendons of origin.

DIFFERENTIAL DIAGNOSIS

The diagnosis is rarely made by clinical means; usually the patient is sent to the roentgenologist as a suspected case of torn medial meniscus, tuberculosis of the knee, or loose body. The other causes of loose body are:

(1) *Synovial osteochondromatosis*. This is a degenerative process involving the synovial membrane with calcification and tendency to form multiple loose bodies; however, in this disease there is no defect apparent in the underlying bone.

(2) *Traumatic loose body* is readily distinguished by the history of a preceding severe trauma and the presence of the bony defect in the most exposed parts of the bone, whereas the osteochondritic lesion is located where it is least susceptible to external violence.

Osteochrondritis dissecans is differentiated from tuberculosis of the knee by the following criteria:

(1) Tuberculosis tends to have much severer symptoms.

(2) The tuberculous joint has in the roentgenogram a generally obscured appearance, while this is not true of osteochondritis dissecans.

(3) In tuberculosis, there is usually a much greater degree of atrophy.

(4) The location of the process is different—in osteochondritis dissecans the areas of the articular surface which have the most contact are involved, while in tuberculosis there is typically early destruction of areas in which there is little or no contact.

(5) Sequestration in tuberculosis shows a sequestrum of increased density which preserves its line of articular cortex, while the surrounding bone is relatively atrophic and the articular cortex indefinite or destroyed; in osteochrondritis dissecans, the articular cortex is intact except in the sequestrated area, and the latter is of a similar or lesser degree of density than the adjacent bone.

In torn medial meniscus, the history and lack of characteristic roentgenographic changes should eliminate osteochondritis dissecans.

Hemophilic joints may at times show multiple, punched-out areas, and usually there is more than one joint involved. The clinical course of acute febrile episodes following trauma, multiplicity of the lesions and evidence of the disease elsewhere should serve to differentiate it.

The defects of skeletal tophi in gout are uncommon in large joints, rarely centrally located and the age incidence is distinct.

TREATMENT AND PROGNOSIS

The treatment of choice is surgical. Fairbank states that the roentgenological dem-

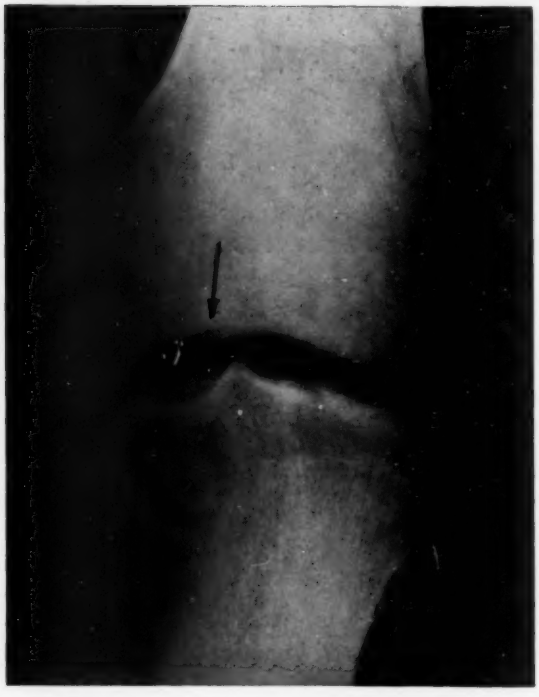

FIG. 1. Note concave appearance at the site of the lesion. No postoperative film could be obtained.

onstration of the lesion alone, unassociated with any symptomatology, does not constitute an indication for opening the joint. In the presence of symptoms, the majority of workers agree that radical extirpation of the detached or partially detached fragment, with or without curettage of the bony bed, is the ideal treatment. The results are almost uniformly good; for example, King in a series of 24 cases reports excellent results in two-thirds and unsatisfactory in only one-tenth. The course even without radical treatment is entirely benign; as our Case III will show, a satisfactory result may be achieved by immobilization alone in those cases in which the urgency of symptoms does not demand immediate surgical interference.

CASE REPORTS

We would like to add 3 cases observed by us to the literature on the subject.

CASE I. A male, aged nineteen, occupation salesman, admitted on July 17, 1937, to the Montreal General Hospital with the history of pain in the left knee for three to four years. The pain occurs on walking any considerable distance or when the knee has been kept in one position for more than a few minutes. It is localized to the joint line just medial to the patella and when most acute may be associated with swelling over the same area. There has been no limitation of motion nor genuine locking. There is no history of preceding trauma (?).

Examination shows slight swelling medial to the patella. A loose mass was felt over the joint line about 1 cm. medial to the patella. There was slight limitation of active extension.

Roentgen examination showed the typical punched-out defect of osteochondritis dissecans located at the lateral aspect of the medial condyle of the femur (Fig. 1).

On July 19, the knee joint was exposed through an internal lateral incision. A small, rounded, elevated area the size of a ten-cent piece was seen on the articular cartilage of the medial condyle of the femur. This was removed completely with the scalpel, exposing raw bone underneath. The bed was not curetted. The medial semilunar cartilage was loose at its anterior attachment, hence it likewise was dissected free and removed. The pathologist reported degenerative non-inflammatory process in cartilage.

Postoperative course was uneventful and the patient was discharged on July 30. In the eight months since operation, he has had no symptoms.

Whether the osteochondritis dissecans or the damaged meniscus was causing the symptoms here cannot of course be ascertained. Our second case, however, gives a history typical of torn medial meniscus; yet the latter was normal and the symptoms due entirely to osteochondritis dissecans.

CASE II. A male, aged nineteen, whose chief complaint was locking of the left knee in flexion, accompanied by severe pain continuing for some hours after the locking itself had been released. This sequence of events had happened with increasing frequency for five years. Physical findings were limited flexion of the left knee with focal tenderness medial to the patella on the articular surface of the femur.

Roentgen examination on July 13, 1936, showed the characteristic annular defect in the articular surface of the medial femoral condyle (Fig. 2).

Fig. 2. Note prominent medial tibial spine.

Fig. 3. *A*, no loose fragment visible; *B*, lesion completely filled in. Immobilization only treatment.

The knee joint was explored on July 14, 1936; necrosis of a dime-sized area on the posteromedial surface of the medial condyle was found involving the articular cartilage and extending into the subjacent bone. The necrotic cartilage and bone were removed; the bed was curetted smooth. The medial semilunar cartilage appeared entirely normal and was not removed. Histological examination of the specimen revealed chronic inflammation of cartilage.

One year and eight months subsequent to operation, the patient was asymptomatic. Re-examination showed almost complete filling in of the operative defect.

The 2 preceding cases were both treated radically, with satisfactory results. Our third case is presented to demonstrate that conservative treatment may be equally satisfactory in some instances.

CASE III. A girl, aged twelve, who, with no history of injury, has complained of weakness and a sensation of "giving way" in the left knee. She has never actually fallen but states that the knee jerks forward and feels as though the bones were being twisted.

Examination revealed a healthy, robust child, walking without any limp or deformity. There is no swelling of the left knee by measurement; however, the lateral pouches appear fuller than those of the right knee. Motion, active and passive, is normal. There is half an inch atrophy of the left thigh. The knee shows some tenderness on pressure over the joint line anteromedially.

Roentgen examination of the left knee on May 23, 1936, showed a punched-out defect of the internal part of the medial condyle with a suggestion of condensation of bone in the articular surface of the tibia opposite.

Patient was placed in a cast subsequently. Re-examination nine months later showed the punched-out area smoother and smaller. Symptoms have entirely disappeared. There was no limitation of motion or pain and no atrophy of the quadriceps.

SUMMARY

(1) The literature pertaining to the etiology, pathology, clinical picture, roentgenological findings, diagnosis and treatment of osteochondritis dissecans has been briefly summarized.

(2) Three typical cases of osteochondritis dissecans of the knee, showing interesting features with regard to diagnosis and treatment, have been added to the literature.

We wish to acknowledge our thanks to Drs. Goldman and Breitman for referring these patients to us.

REFERENCES

1. BALENSWEIG, I. Osteochondritis dissecans of the knee. *J. Bone & Joint Surg.*, 1925, *7*, 465–468.
2. BERNSTEIN, M. A. Osteochondritis dissecans. *J. Bone & Joint Surg.*, 1925, *7*, 319–329.
3. FAIRBANK, H. A. T. Osteo-chondritis dissecans. *Brit. J. Surg.*, 1933, *21*, 67–82.
4. FREIBERG, A. H. Osteochondritis dissecans. *J. Bone & Joint Surg.*, 1923, *5*, 3–17.
5. GEYMAN, M. J. Osteochrondritis dissecans. *Radiology*, 1928, *11*, 315–319.
6. GHORMLEY, R. K. Pathologic changes in diseases of joints. AM. J. ROENTGENOL. & RAD. THERAPY, 1933, *29*, 729–735.
7. KING, D. Osteochondritis dissecans. *J. Bone & Joint Surg.*, 1932, *14*, 535–544.
8. MILLER, L. F. Osteochondritis dissecans of capitellum of humerus. *Radiology*, 1936, *27*, 237–239.
9. RICHARDS, G. E. Osteochondritis dissecans. AM. J. ROENTGENOL. & RAD. THERAPY, 1928, *19*, 278–284.
10. SOMMER, R. Die osteochondritis dissecans (König). *Beitr. z. klin. Chir.*, 1923, *129*, 1–60.

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IRRADIATION OF THE LONG BONES FOR GYNECOLOGIC BLEEDING*

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FUNCTIONAL uterine bleeding is of perennial interest because of its frequency in gynecologic practice. A perusal of hospital charts reveals various diagnoses such as "ovarian insufficiency," "endocrine imbalance," "glandular cystic hyperplasia," "idiopathic or functional menorrhagia," etc., for unexplainable abnormal uterine bleeding. Many well-defined groups have been classified which respond to specific treatment. There is, however, one group of patients exhibiting this symptom which have defied the usual methods of treatment and have defied diagnosis as to its etiology.

All who have treated this condition have found a certain proportion of cases in which all orthodox treatment has been used without result. By orthodox treatment we include the use of uterine styptics, endocrine hemostatics such as antuitrin S, progestin, thyroid extract, and curettage with or without intra-uterine radium.

A few years ago one of us, in calling for a complete blood count in a case of long continued intractable uterine bleeding, received a pathological report which included the blood platelet count. With the exception of a slight secondary anemia, the platelet count was the only abnormal finding. This seemed to be significant in view of the fact that there were no abnormal anatomical findings and that every known method of treatment listed above had been used unsuccessfully. Because of its efficacy in idiopathic thrombocytopenia purpura, irradiation of the spleen was instituted with immediate startling results. Not only did the uterine bleeding cease abruptly after a continuance of at least two years, but the blood platelet count returned to normal and subjectively the patient experienced a new sense of well-being. Therefore, in all cases of functional bleeding we have had blood platelet examination in order to segregate this intractable group of cases.

We have been unable to find in the literature any attention being given to the dyscrasia of the blood platelets in relation to this condition. In the Year Book of Obstetrics and Gynecology for 1937 we have found the following abstract entitled, "Irradiation of spleen for gynecologic bleeding."

At the Berlin Woman's Clinic, P. Caffier observed twelve girls with juvenile hemorrhages during 1926 to 1934 who were treated by means of x-rays applied to the spleen. In five cases there was complete success, and in four cases temporary relief. In four of the five permanently successful cases not only did bleeding cease after two to three days but the menstrual periods became regular. This treatment is harmless and may be used at any age. It probably acts by producing a breakdown of thrombocytes. The author believes that this form of therapy should be combined with modern hormone therapy directed at the cause of bleeding.

Caffier also suggests irradiation of the spleen for bleeding which is due to uterine myomas, especially when roentgen ray treatment locally applied to the fibroids does not bring about a sufficiently rapid cessation of bleeding. The action of irradiation of the spleen is rapid. The author has seen bleeding stop six hours after treatment, hence he believes that this treatment should be used whenever prompt cessation of uterine bleeding is imperative.

It is noteworthy that in this abstract no mention is made of the blood platelet count as a diagnostic or therapeutic aid.

Baer states,

Thrombocytopenic purpura, one of the rare diseases, may present in addition to the usual extravasations, bleeding from the uterus. The diagnosis is based on the decreased platelet count, increased bleeding time and clinical

* Read at the Twenty-fourth Annual Meeting, American Radium Society, St. Louis, Mo., May 15–16, 1939.

manifestations. The best available treatment is repeated blood transfusions. In the more severe instances of the disease splenectomy has been performed.

We know that splenectomy, although usually associated with remarkable improvement in cases of thrombocytopenic purpura, may also be of no benefit. In those cases when the spleen is overactive and destroys the platelets its removal is indicated. We think that in these cases the disturbance in the production of the platelets is in the bone marrow and splenectomy is of no value.

Wright has shown that the megakaryocytes perform the extremely important function of giving rise to the blood platelets. The blood platelets commonly vary between 200,000 and 600,000 per cubic millimeter. The age of the individual causes the red cells and platelet count to vary toward the high normal level in infancy and childhood and to swing toward the low level after the fiftieth year.

Minot pointed out that in certain purpuras any agent bringing about red cell destruction operates against the platelets and megakaryocytes. The platelets ordinarily vary in number in proportion to the vigor of the red cell formation, and at the moment of examination they may be greatly reduced independently of the red cell change. The cause of this destructive process has not been determined. The fact that Lee and Robertson by repeated injections of guinea pig platelets into rabbits have succeeded in producing serum which would destroy the platelets of the guinea pig with consequent purpura is of interest in this relation.

Because there were no other symptoms of purpura in cases under consideration it seemed reasonable that the diminution in the number of platelets was due to a deficient formation in the bone marrow rather than in an increased destruction by the reticulo-endothelial system (primarily the spleen). Therefore, irradiation of the long bones was instituted rather than the irradiation of the spleen. There being no general symptoms of purpura to indicate a diagnosis we have designated this condition as uterine purpura.

We report herewith a few typical cases:

CASE I. M. M., aged twenty-one, single.

Family history negative. Past history: tonsillectomy 1929, appendectomy 1934. Menses began at the age of fifteen, irregular and always late and scanty. Present illness began two years ago with uterine bleeding. Has had four curettements and two applications of radium, at each time was given 1,500 mg-hr. filtered through 1 mm. of platinum. Patient did not know exact dates. This only improved her condition temporarily. Physical examination on May 8, 1936, showed no demonstrable abnormalities. Blood examination was essentially negative except that the platelet count was 91,000.

Date	Platelet Count	Treatment
5-8-36	91,000	.....
5-9-36	.....	100 r to each femur
5-10-36	120,000	100 r to each tibia and fibula
5-11-36	160,000	100 r to each femur
5-12-36	240,000	100 r to each tibia and fibula
5-13-36	290,000	.....

Menses were normal for six months. Following the menses on November 2, 1936, she continued to bleed. Platelet count on November 16, 1936 was 86,000.

11-16-36	86,000	.....
11-17-36	.....	100 r to each femur
11-18-36	132,000	100 r to each tibia and fibula
11-19-36	170,000	100 r to each femur
11-20-36	220,000	100 r to each tibia and fibula

Menses returned to normal and were of the twenty-eight day type and of five day duration. They remained normal until patient moved away in October, 1938.

CASE II. M. S., aged twenty-one, single.

Patient has had continuous uterine bleeding for two years. Past history and family history negative, no surgery except tonsillectomy. Menses began at the age of thirteen, always irregular and tended to be scanty rather than profuse. Two years ago continuous uterine bleeding began. All usual treatments were used without results, including two curettements. During this time patient has had a sense of ill-being, with a feeling of lassitude and was easily fatigued. Physical examination negative.

Blood examination November 23, 1937, reported by Dr. Kretschmer was as follows:

Red blood count 4,240,000; hemoglobin 96 per cent; white blood count 11,300; platelet count 28,000.

Date	Platelet Count	Treatment
11-23-37	28,000	.....
11-24-37	.....	100 r to spleen
11-27-37	101,000	100 r to spleen
11-29-37	82,000	.....
12- 1-37	78,000	.....
12- 2-37	.....	100 r to each tibia and fibula
12- 3-37	124,000	.....
12- 4-37	.....	100 r to each femur
12- 7-37	270,000	.....
12- 9-37	Menses now normal	
12-30-37	65,000	100 r to each tibia and fibula
1- 3-38	.....	100 r to each femur
1- 5-38	144,000	.....
1- 6-38	.....	100 r to each tibia and fibula
1-11-38	155,000	.....
1-13-38	.....	100 r to each femur
1-19-38	178,600	.....
1-30-38	Married. Last report menses normal	
9-29-38	182,000	Has not menstruated since 5-28-38. Pregnant
11-23-38	112,000	.....
2- 1-39	199,000	.....

The coagulation time on November 23, 1938, was 4 min. 30 sec., and on February 1, 1939, was 4 min. 35 sec.

Patient had no treatments after January 13, 1938, and had no disturbance of menses. She was married on January 30, 1938, became pregnant in May and during the pregnancy the platelet count dropped as shown above. She was delivered March 5, 1939, of a normal healthy child. Patient refused to have any more blood counts.

Case III. Mrs. A. I., aged twenty-six.

No serious illnesses. Menses began at the age of twelve and were regular until the age of fifteen. They were of the twenty-eight day type, four days' duration. At fifteen began to menstruate every two weeks. At the age of sixteen began to spot some every day, continuing for two years. She was sent to a lower altitude but continued to be irregular. Ergot was given but this did not change the menses. She was curetted at the age of nineteen, following which menses were regular for six months, then the irregularity returned. Anterior pituitary-like hormone and other hormones were given with no change in the spotting. In 1935, she was curetted again and a cystic tumor was removed from the ovary. Menses were regular for six months and then symptoms recurred. It was then reported that the curettage findings showed a hyperplasia. Physical examination showed no demonstrable abnormalities. On August 23, 1938, patient was given 300 r anteriorly over the uterus and ovaries. August 26, 1938, patient was given 300 r posteriorly over the uterus and ovaries.

Patient had normal menses on September 5 and had no spotting. She reported October 15 that she had had no menses or spotting. October 25 patient began to have pain in the lower right abdomen.

The Aschheim-Zondek test was negative. October 31 exploratory laparotomy revealed tubal pregnancy. The right tube and ovary were removed. Menses in November were normal. Menses in December were of fourteen days' duration. Menses in January were irregular and patient continued to spot. She was given snake venom solution with no improvement. She was again referred for therapy. The blood examination on February 4, 1939, reported by Dr. Kretschmer was as follows: Red blood count, 4,890,000; hemoglobin, 92 per cent; white blood count, 7,200; small lymphocytes, 24 per cent; large lymphocytes, 12 per cent; neutrophiles, 61 per cent; eosinophiles, 1 per cent; monocytes, 2 per cent. There was a very slight poikilocytosis and a slight anisocytosis. The platelet count was 189,320. Coagulation time was 6 minutes and 40 seconds.

Date	Platelet Count	Treatment	Coagulation Time
2- 4-39	189,320	100 r to each femur	6 min. 40 sec.
2- 8-39	.....	100 r to each tibia and fibula	.....
2-13-39	.....	100 r to each femur	.....
2-14-39	Spotting ceased		
2-17-39	.....	100 r to each tibia and fibula	.....
2-20-39	.....	100 r to each femur	.....
2-24-39	134,000	100 r to each tibia and fibula	5 min. 20 sec.
2-27-39	Normal menses		
3- 8-39	.....	100 r to each femur	.....
3-29-39	148,000	.....	6 min. 30 sec.
3-29-39	No spotting or menses since 2-27-39		
4-28-39	No spotting or menses since 2-27-39		

This case did not show any marked change in platelets but nevertheless her abnormal

bleeding ceased. Patient has gained 5 pounds and is still under observation.

CASE IV. P. S., aged thirteen.

Patient had no operation or serious illness. Menses began at the age of eleven and were of five days' duration. Menses were regular until two months ago when they changed to every two weeks and four day duration. No other symptoms. Physical examination negative. Blood examination on May 11, 1938, reported by Dr. Kretschmer was as follows:

Red blood count, 4,820,000; hemoglobin, 90 per cent; white cell count, 13,600; neutrophiles, 71 per cent; small lymphocytes, 17 per cent; large lymphocytes, 4 per cent; eosinophiles, 2 per cent. Coagulation time 7 minutes and 30 seconds. Platelet count was 197,000. On June 13, 1938, platelet count was 110,000.

Date	Platelet Count	Treatment	Coagulation Time
6-13-38	.....	100 r to each femur	4 min. 50 sec.
6-15-38	193,000	100 r to each tibia and fibula	3 min. 50 sec.
6-21-38	154,500	100 r to each femur	4 min. 10 sec.
6-28-38	173,000	100 r to each tibia and fibula	3 min. 15 sec.
7- 2-38	149,000	.....	3 min. 30 sec.
7- 8-38	270,000	.....	4 min. 15 sec.
7-10-38	Normal menses		
7-20-38	280,000	.....	3 min.
8-15-38	213,200	.....	4 min. 10 sec.
8-29-38	253,000	100 r to each femur	2 min. 30 sec.
9- 6-38	199,000	.....	3 min.

The menses became regular and have continued to be regular twenty-eight day type and of five days' duration. Patient has no symptoms.

We have treated several cases empirically with snake venom solution (cobra H.W.D.) using 1 cc. hypodermically three times weekly. The following is a typical case.

CASE V. R. B., aged nineteen.

Family history: mother died in patient's early childhood, no knowledge of her menses. There are three sisters of whom one had some type of menstrual disturbance which soon became normal. Past history: for other illnesses essentially negative. Menses began at the age of fourteen, were irregular for three years, regular for one year, and again irregular until October, 1938, when uterine bleeding became constant although variable in amount. Physical examination showed no demonstrable abnormalities.

Date	Platelet Count	Coagulation Time
12-12-38	121,000	5 min.
12-19-38	191,000	6 min.
12-27-38	199,500	4 min. 15 sec.
1- 3-39	158,000	4 min. 45 sec.
1-10-39	198,000	4 min. 30 sec.
1-17-39	165,000	10 min.
1-24-39	153,000	6 min. 20 sec.
2- 1-39	181,000	5 min. 50 sec.

Menses last of December and January were normal. Menses in February became continuous and irradiation was begun over the long bones.

Date	Platelet Count	Treatment	Coagulation Time
3- 6-39	106,000	.....	5 min. 15 sec.
3- 7-39	.....	100 r to each femur	.....
3-11-39	.....	100 r to each tibia and fibula	.....
3-14-39	.....	100 r to each femur	.....
3-18-39	.....	100 r to each tibia and fibula	.....
3-21-39	125,000	100 r to each femur	3 min. 45 sec.
4-18-39	156,000	.....	3 min. 30 sec.

Menses returned to normal twenty-eight day type and of five days' duration.

Technique Used.

Case I: 200 kv., 50 cm. distance; filtration 0.5 mm. copper and 1 mm. aluminum. Field, 4×10 inches, focusing over the middle of each femur and each tibia.

Case II: Same as Case I except filtration was 0.75 mm. copper and 1 mm. aluminum.

Cases III, IV and V: 200 kv., 50 cm. distance, filtration 1.75 mm. copper and 1 mm. aluminum. Field, 10×20 cm., focusing the same as in Case I.

While studying Case I (a student nurse), we had platelet counts made on a group of normally menstruating nurses. These girls were chosen because of no stigmata of endocrine dyscrasias. Of these, 10 showed above 200,000 platelets and 2 showed below 200,000 but above 150,000 platelets. It

is our impression that uterine bleeding does not occur in the early months of platelet anemia. We feel that it is the long continued deficiency which tends toward the production of bleeding. We must also consider that platelet anemia may be an effect of long continued bleeding with a fatigue of some elements of the hemopoietic tissue and that treatment as described restimulates the production of the platelet precursors. We have not been able to determine any critical platelet level at which bleeding constantly appears. In this connection we must not lose sight of the effect of the individual's endocrines in affecting the situation. It may be that individuals with high blood estrin concentrations would have bleeding with only a small platelet deficiency while those with low estrin concentrations or estrin concentrations balanced by progestin would have bleeding only at lower platelet levels. The same may also be true in thyroid variation. It may be significant that 90 per cent of the cases we have studied were under twenty-five years of age.

The effect of platelet anemia on the maintenance of pregnancy has not been investigated adequately because of a lack of material. One of the cases reported in detail above experienced a normal pregnancy even though the platelet count decreased to 112,000 returning spontaneously before delivery to 199,000.

Another case treated for this type of bleeding with successful recovery showed a marked decrease in platelet count in the third month of pregnancy. She miscarried in the fifth month in the Denver General Hospital and no record of the platelet count was obtainable.

Still another case showing intermittent spotting beginning at her second month of pregnancy was treated with progestin and vitamin E. She began more active bleeding in the fifth month. The platelet count then was 50,000. She was treated with snake venom solution 0.5 cc. three times daily with a consistent rise in platelet count to 260,000 in five days. She miscarried, however, on the same day her platelet count reached normal. The placenta showed evidence of separation during this five day period. One month following the miscarriage she began what she considered a menstrual period which was excessive. Her platelet count at that time was 58,000. She is under radiation treatment at the present time.

We have had no experience in these cases with the use of vitamin K or the antimenorrhagic factor from liver recently introduced. It would be interesting if those who are experimenting with these substances in the treatment of uterine bleeding would check platelet counts and determine whether therapeutic effect and increased platelets are coincidental. We realize that error is great in determining platelets. Dr. O. S. Kretschmer who examined the blood in our series has developed a method by which in multiple counts they correspond within 10 per cent.

CONCLUSIONS

1. We have described a group of cases of functional uterine bleeding which have been intractable to all ordinary forms of treatment. These cases have shown a decrease in the platelet count as the only positive abnormal finding.

2. Treatment of the long bones by small doses of radiation has in almost all instances relieved the bleeding.

3. The cessation of symptoms has been coincidental with a return of the normal platelet count.

4. We have used snake venom solution with similar immediate results but with less prolonged effect.

5. Since there are no other abnormal general findings or other specific symptoms of purpura, we have designated the condition as uterine purpura.

REFERENCES

1. Baer, J. L. Benign uterine bleeding. *Surg. Clin. North America*, 1939, *19*, 149–160.

2. Caffier, P. Zur Frage der Milzbestrahlung bei gynäkologischen Blutungen. *Zentralbl. f. Gynäk.*, 1937, *61*, 1874–1876.

3. LEE, R. I., and ROBERTSON, O. H. Effect of antiplatelet serum on blood platelets and the experimental production of purpura hemorrhagica. *J. Med. Research*, 1916, *33*, 323–336.
4. MINOT, G. R. Diminished blood platelets and marrow insufficiency; a classification and differential diagnosis of purpura hemorrhagica, aplastic anemia and allied conditions. *Arch. Int. Med.*, 1917, *19*, 1062–1084.
5. WRIGHT, J. H. The histogenesis of blood platelets. *J. Morphol.*, 1910, *21*, 263–278.

DISCUSSION

DR. ABRAHAM STRAUSS, Cleveland, Ohio. I would like to ask if any of these patients had large spleens and what the indication was for irradiation rather than splenectomy.

DR. WILLIAM P. HEALY, New York City. I would like just to comment on one point, and that is that these women are all apparently very young, and any form of therapy that will permit us to keep radiation out of the pelvis and yet control the disease is worth while, because we know that intra-uterine irradiation is to be avoided on account of its deleterious effect upon ovarian activity.

It was interesting to me, however, to note that in one of the cases that was reported in this series to have conceived and gone to term, the patient before coming under Dr. Bouslog's and Dr. Evans' observation was said to have been treated twice with intracavitary irradiation amounting to 1,500 milligram-hours each time without controlling the uterine bleeding, and subsequently conceived and went to term and was delivered of a normal baby.

Of course that is an item that should be received a little skeptically (as to the amount of irradiation, etc.), at least from our angle.

I still would like to say that keeping irradiation out of the pelvic field in these young women is important.

I am extremely interested in the essayists' paper and in their results and findings. Irradiation of the spleen has been the form of treatment that we have usually carried out in these cases with a fair degree of success. In only one case have I used snake venom and that patient had a general purpuric reaction, of the other mucous membranes as well as the uterine, and she also had curettage and small transfusions. She responded at once and satisfactorily to the snake venom serum. Bleeding terminated and menses became normal.

DR. EVANS (closing). This has been an interesting series of cases to Dr. Bouslog and myself in that we were unable to find anything in the literature concerning this particular group of cases.

In answer to the question about the spleen, there were no enlargements of the spleen in any of the cases that we saw, and the cases were not serious enough to consider splenectomy.

One point I want to stress is that there is apparently no critical level of platelet count. That, as we tried to bring out in the paper, is probably due to hormonal variation of the individual.

In comparing this treatment to the treatment with snake venom, the snake venom apparently brings up the platelet level very rapidly and the uterine bleeding usually ceases, but within a few weeks of the cessation of the snake venom treatment, the platelets drop down to their low level again and bleeding recurs.

It has been our impression that, while in every case the first group of radiation treatments has not completely relieved the individual, the relief has been of longer duration and that subsequent irradiation has given apparent cure over a much longer period of time.

The value of this, as Dr. Healy has said, is because we find it in young women and we do not have to destroy the reproductive function.

Another group of cases that is interesting to me is the group of women who miscarry for no reason: Those whom we have always told that they had an imperfect implantation or an infantile uterus or some such excuse in order to allay their apprehension. We haven't had enough cases yet to know whether this is a factor in miscarriage or not.

It is very likely, however, that there is a certain group of women who miscarry, in which the cause is due to this platelet count. From now on I am going to have platelet counts taken on all women who present themselves as obstetrical cases.

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POST-IRRADIATION CHANGES IN THE LUNGS AND THORAX

A CLINICAL, ROENTGENOLOGICAL AND PATHOLOGICAL STUDY, WITH EMPHASIS ON THE LATE AND TERMINAL STAGES*

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RADIATION damage to the lungs and pleura has been observed and reported by numerous radiologists since Groover, Christie and Merritt directed attention to this complication. Prior to this study, only a few unsubstantiated reports were published of such injury. These clinical observations have been corroborated by careful animal experimentation by many investigators. An exhaustive search of the literature has not revealed any records of patients, so injured, who were followed for many years. has been selected because of special features we wish to present. Of the 18 cases, 11 died and postmortem studies were done on 8.

The case histories of all the patients follow. Included are the details of dosage, the relevant clinical features and roentgen studies, and finally, the postmortem findings where this examination was made.

CASE REPORTS

CASE 1. A. B., female, aged forty-six* (Table 1).

TABLE I

Year	Month	Field	Dose	Kv.	Ma.	Filter	Dist.
1934–1935	12/8–1/26	L. ant. axilla and supraclavicular	1600 r† each	200	8	0.5 mm. Cu plus 1 mm. Al	50 cm.
		L. post. axilla and supraclavicular	2000 r each	200			50 cm.
		L. axilla directly	300 r	200			50 cm.
		L. ant. chest wall 20×20 cm.	1000 r	200			50 cm.
		L. ant. chest wall 20×20 cm.	1000 r	140	8	4 mm. Al	50 cm.

It is the purpose of this paper to describe the roentgen, clinical and pathological findings of all the stages of radiation damage to the lungs. Outstanding among the late manifestations in several cases is the terminal picture of severe pulmonary fibrosis associated with signs of right heart failure. The latter has not, as yet, been described in the literature on radiation pneumonitis.

MATERIAL

The material to be presented consists of 18 cases, which were followed for periods up to twelve years following treatment. This series does not represent all the cases of pneumonitis observed in our clinic but

Status on Admission, December 8, 1934. Postoperative carcinoma of the left breast referred for prophylactic irradiation.

Treatment. One course of moderately intensive irradiation. Average dose, high voltage 250 r, medium voltage 175 r.

Course. Sticking pain appeared in the left chest five weeks following irradiation. Roentgenograms of the lungs now showed linear infiltrations in the left hilum. During the next two months, films showed increase in the left hilar infiltrations, tenting of the left diaphragm and adhesions between the pleura, diaphragm and heart on the left. Fever, sweating and severe precordial pain appeared six months after

* Case taken from Dr. Freid's private practice.

† For all case reports r measurements are in air unless otherwise indicated.

* Read in part before the New York Roentgen Ray Society, New York City, March 20, 1939.

FIG. 1. Case 1. Pleural, pericardial and interlobar effusions six months following irradiation.

FIG. 2. Case 1. Few hilar infiltrations persist. Pericardial, pleural and interlobar effusions completely absorbed.

irradiation. Dry cough and dyspnea followed soon thereafter. Films now showed partial resolution of the hilar infiltrations, less tenting of the left diaphragm, slight left interlobar pleurisy and pericardial effusion. Sticking pain appeared in the left medial chest nine months after irradiation. From this point on, symptoms and roentgenograms of the chest showed progressive improvement. Two years later, the patient had no complaints, and roentgenograms of the heart and lungs were practically normal. The skin now showed moderate telangiectasia.

CASE II (Monte. Hosp. Rad. Cl. No. 3675). P. B., male, aged forty-three (Table II).

Status on Admission, October 7, 1937. Carcinoma of the left upper lobe bronchus.

Treatment. Intensive irradiation given, cross-firing lesion from several fields. Two fields daily, each receiving 250–300 r, treated November 19, 1937; thereafter only single fields.

Course. Initial cough and pain disappeared immediately following irradiation. One month later, the patient developed cough, dyspnea and fever. The original lesion, on roentgen examination, had been noted on the left side, between the 3rd and 4th ribs. By November 1, 1937, it had receded under therapy. The follow-up film of January 22, 1938, showed a number of soft irregular infiltrations in the treated lung field, also some clear honeycombed areas, the largest suggesting a cavity. With the recurrence of cough on January 30, 1938, patient developed pneumonic signs in the involved area and severe dyspnea. He died of a pulmonary hemorrhage, six weeks after irradiation.

*Postmortem Examination.** The left lung was homogeneously gray; below the upper lobe bronchus was a large cavity containing foul

* We are indebted to Dr. Fülstow, pathologist to the Norwalk Connecticut General Hospital, for the postmortem findings.

TABLE II

Year	Month	Field	Size	Dose	Kv.	Ma.	Filter	Dist.
1937 I	10/7– 10/29	L. ant. chest, upper L. post. chest, upper	15×15 cm. 15×15 cm.	3400 r 3100 r	200	25	1 mm. Cu plus 4 mm. Al	80 cm.
1937 II	11/4– 12/23	L. ant. chest, upper and inner L. ant. chest, upper and outer L. post. chest, upper and inner L. post. chest, upper and outer L. ant. lat. chest L. post. lat. chest	10×8 cm. 10×8 cm. 10×8 cm. 10×8 cm. 10×10 cm. 10×8 cm.	900 r 900 r 1200 r 1200 r 3000 r 2700 r	200	25	1 mm. Cu plus 4 mm. Al	80 cm.

Fig. 3. Case II. Mass in the left lung extending out from the left hilum.

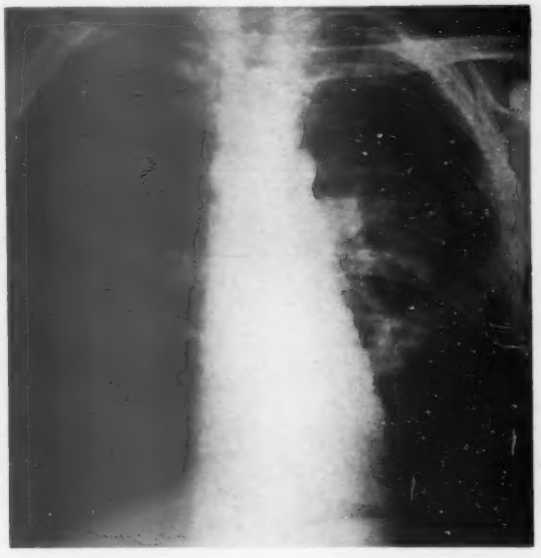

Fig. 4. Case II. Following irradiation. Number of soft irregular infiltrations in the medial half of the left lung. Few areas of rarefaction in this region suggesting cavitation.

pus; the bronchi were filled with blood clots. Microscopic study revealed bronchopneumonia with purulent bronchitis, and numerous foci of necrosis. Fibrosis masked the picture, so that no definite carcinoma could be seen.

Case III (Monte. Hosp. Rad. Cl. No. 2305). H. B., female, aged thirty (Table III).

Status on Admission, April 28, 1933. Lymphosarcoma involving the left tonsil, left cervical nodes and right mediastinum.

Treatment. Daily dose 250 and 330 r first course; 250 r other courses.

Course. Roentgenograms ten days following Course I showed a few infiltrations in the right upper medial lung. About five weeks later, patient developed pain in the right posterior chest and a productive morning cough. Roentgenograms now showed many fluffy infiltrations in the upper right lung. Symptoms and infiltrations disappeared over a period of three months. The patient then developed left supraclavicular nodes and slight widening of the left superior mediastinum. Following Course II, cough reappeared, also general malaise. Two months following Course III, roentgenograms showed further widening of the left superior mediastinum, infiltrations in the adjacent left lung and tenting of the left diaphragm. The patient now developed bilateral bronchopneumonia and died two weeks later.

Case IV (Montefiore Hospital No. 18123). F. G., female, aged nineteen (Table IV).

Status on Admission May 10, 1929. Hodgkin's disease involving supraclavicular and mediastinal nodes.

Table III

Year	Month	Field	Size	Dose	Kv.	Ma.	Filter	Dist.
1933 I	4/28– 5/21	R. and L. ant. mediastinum Post. mediastinum	15×8 cm. 15×12 cm.	1880 r each 1640	200	30	0.5 mm. Ag plus 1 mm. Al	50 cm.
1933 II	10/10– 10/26	L. supraclavicular region	7×9 cm.	2000 r	200	4	0.5 mm. Cu plus 1 mm. Al	50 cm.
1933 III	11/14– 12/15	L. ant. mediastinum L. post mediastinum	10×15 cm. 10×21 cm.	1900 r 1480 r	200	4	0.5 mm. Cu plus 1 mm. Al	50–80 cm.

TABLE IV

Year	Month	Field	Size	Dose	Kv.	Ma.	Filter	Dist.
1929 I	5/14–6/28	L. ant. and post. chest R. ant. and post. chest	16×13 cm. 20×12 cm.	1800 r each 1725 r each	200	30	0.5 mm. Ag plus 1 mm. Al	50 cm.
1929 II	8/13–9/4	L. ant. and post. chest R. ant. and post. chest	16×13 cm. 20×12 cm.	1650 r each 1650 r each	200	30	0.5 mm. Ag plus 1 mm. Al	50 cm.
1929 III	9/25–12/12	R. and L. post. chest	20×12 cm.	2500 r each	200	30	0.5 mm. Ag 1 mm. Al	50 cm.

Treatment. Individual doses varied from 250 to 330 r.

Course. Mediastinal nodes smaller and general condition improved after first course of irradiation. Dyspnea and slight cough present on admission persisted. Following second course of radiotherapy, patient gradually declined, although roentgenograms showed further recession of the mediastinal nodes. Dyspnea and cough were worse and pain appeared in the chest. Roentgenograms now showed soft infiltrations in the lower two-thirds of both lungs, slight elevation of the left diaphragm, a few pericardio-diaphragmatic adhesions and slight enlargement of the heart. The third course of irradiation was given because the pneumonitis was not recognized. One month later, patient developed tachycardia, palpitation and cyanosis. She died within a few weeks with symptoms of diffuse bronchopneumonia.

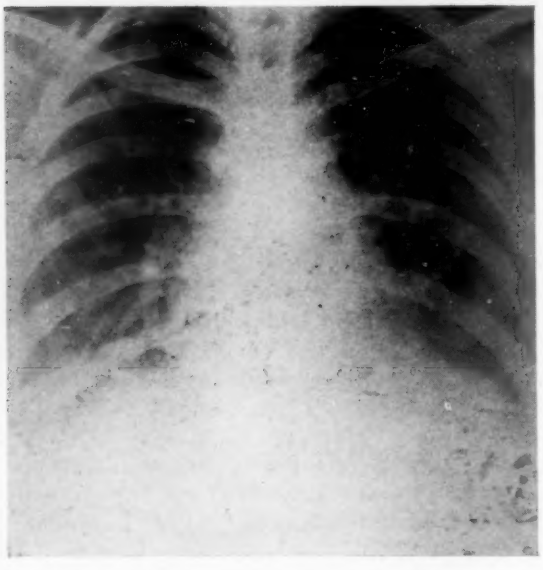

FIG. 5. Case IV. Soft infiltrations lower two-thirds of both lungs.

Postmortem Examination. The lungs showed atelectasis, patchy cellular fibrosis, areas of hyalinization and hemorrhage, also bronchiolar dilatation. The lymph nodes were diffusely fibrotic. A small effusion was present in the pericardium. The right auricle and ventricle were increased in size. The left heart was negative.

CASE V (Montefiore Hospital No. 29005). E. B., female, aged forty-two (Table V).

Status on Admission, January 7, 1938. Unoperated carcinoma of right breast; post-irradiation. No evidence of local or distant disease at this time. Some pain present over the right upper chest.

Treatment. The irradiation was all given at another institution. The original mass in the breast had completely receded.

Course. Dry cough and right shoulder pain

TABLE V

Year	Month	Field	Dose	Kv.	Ma.	Filter	Dist.
1937	5/28–6/25	R. breast, upper R. breast, lower R. breast, lateral R. supraclavicular region R. axilla, direct The five fields were treated in rotation, 250 r per treatment	2000 r 2000 r 2000 r 2000 r 2000 r	200	30	0.5 mm. Cu plus 1 mm. Al	50 cm.

Table VI

Year	Month	Field	Size	Dose	Kv.	Ma.	Filter	Dist.
1934 1935	11/28– 1/2	Ant. mediastinum Post. mediastinum	15×15 cm. 15×15 cm.	2100 r 2100 r	200	30	0.5 mm. Ag plus 1 mm. Al	50 cm.

were noted three months following radiotherapy, lasted seven to eight months, and then disappeared. A chest film, taken four months after irradiation, showed some fibrosis of the right upper lobe which had been clear before treatment. The fibrosis became sharper in appearance on later films. The skin showed induration and some telangiectasia. The patient later developed skeletal, pulmonary and cerebral metastases in the order named, and died in August, 1939.

Case vi (Montefiore Hospital No. 26217). P. C., female, aged fifty-five (Table vi).

Status on Admission November 23, 1934. Lymphoblastoma of the mediastinum with symptoms of mediastinal compression.

Treatment. One field daily. Dose 100 r at onset; later 150 r.

Course. Immediately following the irradiation, the lungs and mediastinum became negative. Roentgenograms ten weeks later showed exaggeration of hilar shadows, streaky infiltrations radiating out from the left hilum, and soft confluent infiltrations in the upper right lung. Cough and dyspnea persisted when mediastinal pressure was relieved, due to appearance of pneumonitis. Onset of pain in the right shoulder radiating down the arm, also right interscapular pain. Roentgen signs increased for six weeks and then slow resolution set in. Roentgenograms three years later show only slight fibrosis in the hilar areas and upper lobes. Occasional nonproductive cough and dyspnea have persisted to the present.

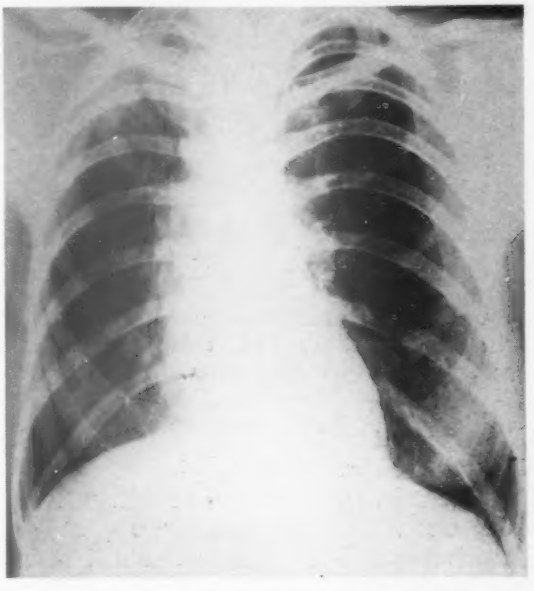

Fig. 6. Case v. Moderate fibrosis of right upper lobe.

Table VII

Year	Month	Field	Size	Dose	Kv.	Ma.	Filter	Dist.
1933 I	4/17– 6/24	R. breast, axilla, supraclavicular	20×20 cm.	1400 r (average dose 400 r)	200	5	0.5 mm. Cu plus 1 mm. Al	50 cm.
1934 II	2/2– 3/13	R. breast, axilla, supraclavicular	20×20 cm.	2000 r (average dose 500 r)	200	5	0.5 mm. Cu 1 mm. Al	50 cm.
1935 III	4/15	R. breast, ant., one exposure R. axilla, direct, one exposure R. axilla and supraclavicular, post., one expos.		750 r 750 r 750 r	200	5	0.5 mm. Cu plus 1 mm. Al	50 cm.
1935 IV	9/23– 9/26	Course III repeated			200	5	0.5 mm. Cu plus 1 mm. Al	50 cm.
1937 V	3/11– 3/17	R. supraclavicular. Radium element pack		24000 mg-hr.				

FIG. 7. Case VIII. Diffuse haziness and fibrosis right upper lobe. Few calcific plaques in right anterior chest wall opposite 2nd and 3rd anterior ribs; 2nd 3rd, 4th and 5th right anterior ribs show old fractures with eburnation of the ununited ends resulting in a type of pseudarthrosis.

CASE VII (Montefiore Hospital No. 29119). C. R., female, aged fifty-five (Table VII).

Status on Admission, January 30, 1938. Postoperative, post-irradiation carcinoma of the right breast.

Treatment. The radiation was administered postoperatively at another institution. The therapy was initiated for swelling of the right neck, interpreted as metastatic nodes. Later treatment was given for residual thickening and swelling of the arm. Doses were massive.

Course. Slight cough and edema of the right arm were present before treatment. These increased markedly after therapy. Axillary pain now appeared. Roentgenograms of November, 1937, showed right upper lobe fibrosis in the previously clear lung. The later films showed the same picture, also a fracture of the 3rd right rib posteriorly, without callus. The patient gives no history of trauma. At present, there is marked telangiectasia of the treated region and the right supraclavicular area is stony hard. The edema of the right arm is very marked, so that the extremity is useless. The lymphedema and skin changes are the outstanding features of this case; the lung symptoms are mild. The patient at present shows no evidence of malignancy.

CASE VIII (Monte. Hosp. Rad. Cl. No. 5088). A. G., female, aged sixty-nine (Table VIII).

Status on Admission, December 13, 1937. Carcinoma of the right breast, excised locally; postoperative irradiation.

Treatment. The radiotherapy was administered at another institution and consisted of massive doses of 500–700 r to large fields. Course I was given before the local excision; Course II, after. Later courses were for edema of the breast, and prophylactically.

Course. The lungs were clear at the onset. By March 8, 1936, cloudiness of the left apex and widened mediastinum were noted. On February 17, 1930, report was "chest positive for metastases." These findings were evidently due

TABLE VIII

Year	Month	Field	Dose	Kv.	Ma.	Filter	Dist.
1924 I	4/4– 4/23 5/10	R. breast, R. axilla, R. lat. breast Single exposures Bare tubes implanted in R. axilla	 700 r each 1650 mc-hr.	200		0.5 mm. Cu plus 1 mm. Al	50 cm.
1924 II	9/18– 10/7 12/2	Course I repeated, excluding radium therapy R. breast and axilla, lat.	 700 r	200		0.5 mm. Cu plus 1 mm. Al	50 cm.
1925 III	3/10– 4/3	R. breast, lower; R. breast, lat.; R. breast, upper	700 r each	200		0.5 mm. Cu plus 1 mm. Al	50 cm.
1926 IV	1/18	R. axilla R. breast, R. axilla, R. supraclavicular	700 r 500 r each	200		0.5 mm. Cu plus 1 mm. Al	50 cm.
1927 V	1/1– 8/5	7 treatments, 500 r each, as follows: R. ant. supraclavicular—3 treatments R. ant. axilla—2 treatments R. breast—2 treatments	 1500 r 1000 r 1000 r	200		0.5 mm. Cu plus 1 mm. Al	50 cm.
1928 VI	6/14	R. ant. breast	600 r	200		0.5 mm. Cu	50 cm.

Table IX

Year	Month	Field	Size	Dose	Kv.	Ma.	Filter	Dist.
1934 I	5/10	Gold seed implants, L. neck		1000 mc-hr.				
1934 II	6/19–6/25	L. supraclavicular, ant., post.; L. direct axilla, average	10×12 cm.	500 r each	198	30	0.5 mm. Cu plus 1 mm. Al	50 cm.
		R. supraclavicular, ant., post.; R. direct axilla, average	10×12 cm.	500 r each				
1934 III	6/26–7/4	Course II repeated			198	30	0.5 mm. Cu plus 1 mm. Al	50 cm.
1934 IV	7/5–7/11	Course II repeated			198	30	0.5 mm. Cu plus 1 mm. Al	50 cm.
1934 V	11/28–12/5	R. breast; R. axilla, post.; R. axilla, direct; and R. lower breast		600 r each	198	30	0.5 mm. Cu plus 1 mm. Al	50 cm.
1934	12/8–12/10	Radium element pack, L. supraclavicular region		23000 mg-hr.				
1935 VI	3/12–3/14	Radium element pack, L. infraclavicular region		24000 mg-hr.				
1935 VII	5/21–5/22	L. upper breast, L. supraclavicular, post.		700 r each	198	30	0.5 mm. Cu 1 mm. Cu	50 cm.

to pneumonitis. At present, there is noted, on the right, fibrosis and large calcific plaques in the upper lobe, tenting of the diaphragm and pleural adhesions. The treated skin shows telangiectasia and induration, and a draining unhealed ulcer in the right axilla. The 2nd, 3rd, 4th and 5th right anterior ribs show old fractures with eburnation of the ununited ends, resulting in pseudarthrosis. No history of trauma. The fractured ribs give no pain. Since the last treatment, eleven years have elapsed without evidence of recurrence or metastases. The ulcer and pain in the right axilla, with restriction of arm motion, are her present chief complaints.

Case IX (Montefiore Hospital No. 29398). N. B., female, aged fifty-six (Table IX).

Status on Admission, April 28, 1938. Postoperative, post-irradiation carcinoma of right and left breasts.

Treatments. All radiotherapy was given at another institution. Large massive doses were used, combined with gold seed implants. Courses II to V were prophylactic postoperative. The radium element pack was applied for residual disease.

Course. Pain appeared in the left side of the neck at the completion of irradiation. The lungs were negative at this time. On April 19, 1938, there was noted some fibrosis in the infraclavicular part of the left lung, destruction of the sternal end of the left clavicle with pathological fracture, fracture of the 2nd left anterior rib,

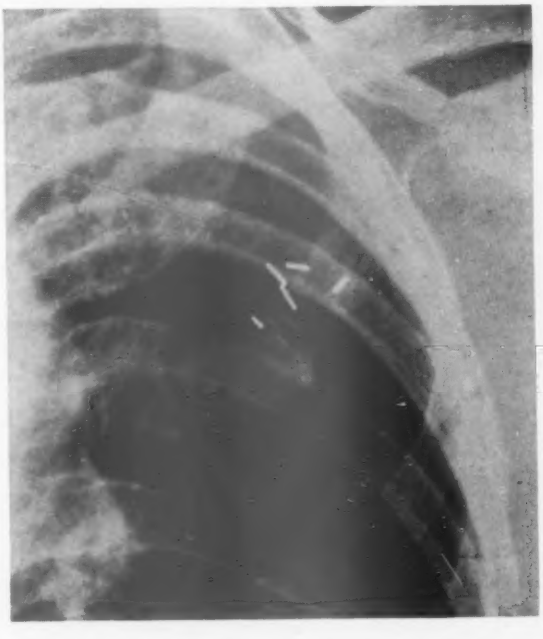

Fig. 8. Case IX. Few fibrotic infiltrations in the left infraclavicular regions. Pathological fracture with overriding of fragments medial third of left clavicle. Fracture of second left anterior rib with non-union.

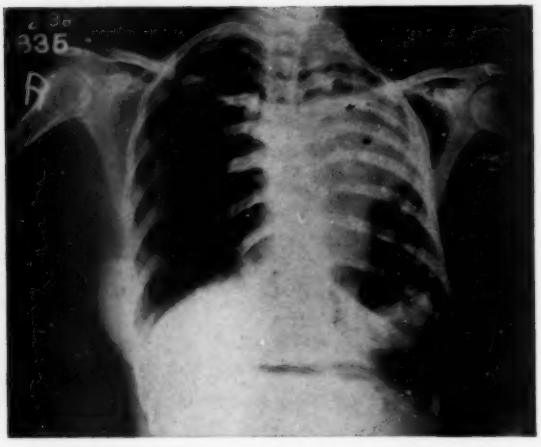

FIG. 9. Case x. Marked fibrosis left upper lobe. Trachea and mediastinum are drawn over to the left. Arrows point to areas of calcification in the supra- and infraclavicular regions in the anterior portion of the lung.

and osteoporosis of the 1st to 5th left ribs. The fractures are ununited. There are telangiectasia and induration of the left infraclavicular region. The patient presents no evidence of metastasis at this time. Both sides received approximately the same roentgen therapy; therefore, the addition of the gold seeds and the radium element pack to the left must be considered the cause of the lung and skin changes, fractures, etc., noted in this area.

CASE X (Montefiore Hospital No. 15012). R. N., female, aged twenty-seven (Table x).

Status on Admission, July 9, 1927. Probable lymphoblastoma involving the left supraclavicular and mediastinal nodes. Left pleural effusion.

Treatment. One treatment daily, dose 250–330 r. The last course was given because the pneumonitis was interpreted as recurrence.

Course. Dyspnea and weakness were present on admission. Later, pain appeared in the left supraclavicular area, also morning cough and palpitation. The original films showed a left mediastinal mass and left pleural effusion. These disappeared following irradiation. A few linear infiltrations were noted on December 9, 1929. They became more marked by February 4, 1930, with the mediastinum drawn to the left. The fibrosis and adhesions showed further progression by October 1, 1930. Course IV was then given and was followed by increased fibrosis and calcific infiltrations in the left upper lobe. These have persisted for the past six years and, in addition, the trachea and mediastinum are pulled to the left and the left dome of the diaphragm is elevated. The roentgen picture of pneumonitis dates from December, 1929. At present, this patient's only complaint is moderate dyspnea on exertion.

CASE XI (Monte. Hosp. Rad. Cl. No. 1773). Z. B., female, aged fifty-one (Table XI).

Status on Admission, March 31, 1931. Lymphoblastoma involving hilar nodes.

Treatment. Average dose 330 r. For the third course 200 r.

Course. Following the first course of irradiation, the hilar nodes became much smaller. Cough appeared one week and dyspnea six weeks following the second course. Roentgeno-

TABLE X

Year	Month	Field	Size	Dose	Kv.	Ma.	Filter	Dist.
1927	7/9–	L. chest, ant.	23×10 cm.	985 r	200	5	0.5 mm. Cu	50 cm.
I	7/30	L. chest, post.	23×14 cm.	1315 r			plus	
		L. chest, lat.		985 r			1 mm. Al	
		Mediastinum and R. chest, ant.		985 r				
		Mediastinum and R. chest, post.		985 r				
		L. supraclavicular, ant.		750 r	130	5	3 mm. Al	40 cm.
1929	1/21–	R. supraclavicular, post.		1640 r	200	30	2 mm. Cu	50 cm.
II	1/31						plus	
							1 mm. Al	
1929–	11/9–	L. chest, upper and medial		1970 r	200	30	2 mm. Cu	50 cm.
1930	1/18	R. chest, upper and medial		1970 r			plus	
III		L. chest, lat.		1970 r			1 mm. Al	
1930	10/11–	Ant. upper chest		1970 r	200	30	2 mm. Cu	50 cm.
IV	12/3	Ant. upper medial chest		1970 r			plus	
							1 mm. Al	

Table XI

Year	Month	Field	Size	Dose	Kv.	Ma.	Filter	Dist.
1931 I	3/31– 4/28	R. ant. and post. chest L. ant. and post. chest Ant. and post. medial chest	20×14 cm. 20×14 cm. 18×15 cm.	985 r each 985 r each 985 r each	200	30	0.5 mm. Ag plus 1 mm. Al	50 cm.
1932 II	3/21– 4/8	Ant. and post. chest	20×18 cm.	2000 r each	200	30	0.5 mm. Ag plus 1 mm. Al	50 cm.
1932 III	10/3– 11/7	R. ant. chest R. post. chest L. ant. and post. chest Ant. and post. mediastinum	20×16 cm. 20×16 cm. 20×16 cm. 20×10 cm.	400 r 200 r 200 r each 985 r each	200	4	0.5 mm. Cu plus 1 mm. Al	50 cm.
1934 IV	1/31– 2/19	Post. medial chest	22×25 cm.	1600 r	200	4	0.5 mm. Cu plus 1 mm. Al	50 cm.

grams now showed infiltrations suggesting fibrosis in the medial portions of both lungs. Five months later, these infiltrations were much more extensive, the diaphragm showed tenting and the heart was increased in size, the appearance suggesting pericardial effusion. Because the pneumonitis and resulting fibrosis were not recognized, the patient was given further irradiation. This was followed by recurrence of the cough, chest pain and increased dyspnea. In January, 1934, roentgenograms showed dense fibrosis with small calcific nodules in both upper lobes, extreme tenting of the diaphragm and mergence of the latter with the heart shadow. The heart was smaller. Later roentgen studies were unchanged. The patient's dyspnea was progressive and especially marked on exertion. Cyanosis and abdominal pain appeared late in the disease. The treated skin showed marked atrophy and telangiectasia. The patient died in June, 1939, with symptoms of right heart failure.

Postmortem Examination. This showed bilateral serosanguineous pleural effusions, marked bilateral thickening of the pleura, fixation and retraction superiorly of the diaphragm and dense adhesion to the anterior chest wall of the anterior mediastinal structures, the anterior pericardium and the root of the great vessels. The lungs presented atelectasis, hyalinizing fibrosis, intense congestion, areas of inflammation and areas with bronchial destruction. Heart failure cells were present in the alveoli. The heart showed marked thickening of the pericardial layers, hypertrophy and interstitial fibrosis of the right ventricle and extensive hyaline replacement with hypertrophy of the remaining fibers of the right auricle. The left heart was normal. No evidence was found of lymphoblastoma.

Case XII (Montefiore Hospital No. 27926). M. B., white male, aged thirty-nine (Table XII).

Status on Admission, February, 1937. A case of Hodgkin's disease in the terminal stages.

Treatment. The roentgen therapy was administered at another institution. Courses I to IV were given for a mediastinal mass, supraclavicular nodes, a mass over the left chest wall and because of cough and shoulder pain. Courses V to VII were given for what was interpreted as Hodgkin's infiltration, though the findings on roentgen examination are those of pneumonitis.

Fig. 10. Case XI. Soft infiltrations in the medial portions of the lungs. Tenting of the diaphragm.

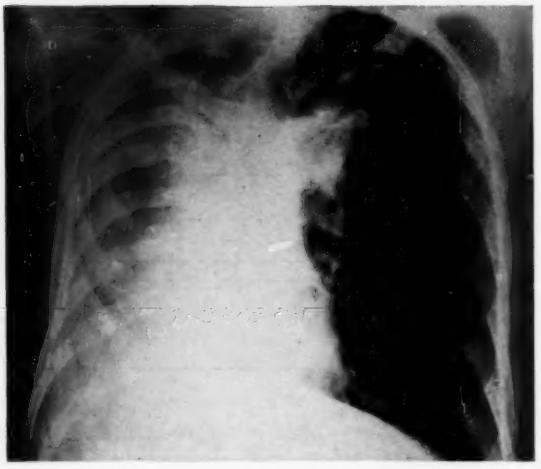

FIG. 11. Case XII. Trachea, heart and mediastinum drawn to right. Marked fibrosis of the right lung. Scattered areas of fibrosis left lung. Right diaphragm elevated.

The single doses were massive, as a rule 450–900 r per treatment.

Course. At the onset of his illness, the patient complained of cough and left shoulder pain. At this time, a mass was present at the right hilum, also a small right pleural effusion. These receded following irradiation. On April 24, 1934, there was noted reappearance of the small right effusion, slight traction of the trachea to the right, and cloudiness of the lower half of the right lung. When admitted to Montefiore Hospital, there was present a productive cough, blood streaked sputum, dyspnea on exertion, and occasional rises in temperature. Roentgenograms of the chest now showed marked fibrosis of the right lung, retraction of the trachea and heart to the right, fibrosis in the left hilum and elevation of the right diaphragm. Cough and chest pain gradually increased. The patient later developed Cheyne-Stokes respiration, dyspnea, tachycardia and cyanosis. Death occurred on May 28, 1938.

Postmortem Examination. Right: The lung was small, fibrotic and airless; the pleura 0.75 cm. thick; the bronchi dilated and purulent. There were scattered patches of bronchopneumonia. The pulmonary arteries were arteriosclerotic. The veins of the hilum were partially or entirely occluded from without by granulation tissue. *Left:* The lung showed less severe but similar pulmonary changes. *Heart:* The pericardium was adherent. The right heart showed hypertrophy and dilatation of the auricle, ventricle and outflow tract. The left heart was negative.

TABLE XII

Year	Month	Field	Size	Dose	Kv.	Ma.	Filter	Dist.
1932 I	3/17– 4/2	R. supraclavicular, ant. R. chest, ant. R. chest, post.	 17×14 cm. 17×14 cm.	2700 r* 2700 r 2700 r	180	4	0.5 mm. Cu plus 1 mm. Al	50 cm.
1933 II	5/18– 5/26	L. chest, ant.	16×14 cm.	2700 r	180	4	0.5 mm. Cu plus 1 mm. Al	50 cm.
1933 III	10/31 11/7	Entire chest, ant. Entire chest, post.		220 r 140 r	180	4	2 mm. Cu plus 1 mm. Al	80 cm.
1934 IV	1/23– 2/7	L. scapula R. scapula	14×14 cm. 7× 9 cm.	4400 r 1200 r	180	4	1 mm. Cu plus 1 mm. Al	30 cm. 40 cm.
1934 V	4/27– 5/11	Entire chest, ant. Entire chest, post.		900 r 900 r	180	4	1 mm. Cu plus 1 mm. Al	75 cm.
1935 VI	2/27– 5/20	L. chest, ant. and upper Post. chest—very large field	10×15 cm.	400 r 300 r	180	4	2 mm. Cu plus 1 mm. Al	60 cm. 80 cm.
1936 VII	3/5– 5/12	L. chest, ant. and upper L. chest, post. Entire chest, post.	Fields very large	800 r 1100 r 300 r	180	4	1 mm. Cu plus 1 mm. Al	50 to 80 cm.

* r with back-scatter.

Microscopically, in addition to the extensive fibrosis, hyalinization, bronchial and vascular changes, there was a slight amount of Hodgkin's infiltration in both lungs.

Case xiii (Montefiore Hospital No. 28028). M. G., male, aged sixty-two (Table xiii).

Status on Admission, June 1, 1938. Carcinoma of the upper and middle third of the esophagus. Gastrostomy. Inactive pulmonary tuberculosis.

Treatment. At another hospital, 300 r to one field daily.

Table XIII

Year	Month	Field	Size	Dose	Kv.	Ma.	Filter	Dist.
1936	1/27–2/28	R. ant. and post. mediastinum L. ant. and post. mediastinum	14×17 cm. 14×17 cm.	2700 r each 2700 r each	198	30	0.5 mm. Cu plus 1 mm. Al	60 cm.

Course. On admission, roentgenograms showed fibrotic infiltrations, due to healed tuberculosis, in the apices and infraclavicular regions. Marked fibrosis was also present in the medial portions of both lungs (the field of irradiation), also pleurodiaphragmatic adhesions. Six months later, there was a marked increase in the pulmonary fibrosis, the right diaphragm was slightly elevated and the left diaphragmatic adhesions had disappeared. Calcifications were present in the right infraclavicular region. Onset, at about this time, of dry nocturnal cough and dyspnea on exertion. Three months later, there was an attack of hemorrhage, pain in the chest, dyspnea, cyanosis and rise in temperature. The patient died the next day with signs of bronchopneumonia.

Postmortem Examination. The lungs were normal in size. The medial portions were adherent to the mediastinum; the posterior portions to the posterior chest walls. In the region of the tracheal bifurcation, trachea, bronchi and aorta were matted together by fibrous tissue. Medially, the lungs were firm and fibrotic; laterally, the parenchyma was normal. The apices showed bilateral healed tuberculosis. Some of the bronchioles were widened and contained mucopurulent exudate. The left lower lobe was congested, slightly edematous, and contained areas of bronchopneumonia. Tuberculosis was found in the hilar lymph nodes. The parietal pericardium was firmly adherent on both sides to the pleura. Musculature of the right ventricle was slightly thickened.

Case xiv (Montefiore Hospital No 28988). G. Z., female, aged forty-five (Table xiv).

Status on Admission, November 8, 1937. Postoperative carcinoma of the right breast.

Treatment. The irradiation was administered at another institution. Dosage was massive. Course iv was given because lung changes due to pneumonitis were interpreted as metastases. Extreme lymphedema necessitated a disarticulation of the right arm in 1934. The excised tissues were negative for carcinoma.

Course. The initial radiotherapy, two years after operation, was to a skin nodule in the right axilla. Dyspnea, chest pain and swelling of the right upper extremity had their onset in 1927, following the roentgen therapy. These increased with further irradiation. In April, 1928, infiltrations about the right hilum due to pneumonitis were interpreted as metastases and further irradiation was prescribed. Complaints and chest findings remained unchanged until 1936, when dyspnea and chest pain suddenly became marked. Roentgenograms now showed infiltrations in the right upper lung and a massive pleural effusion which on aspiration contained carcinoma cells. The skin and tissues of the right supraclavicular region and shoulder

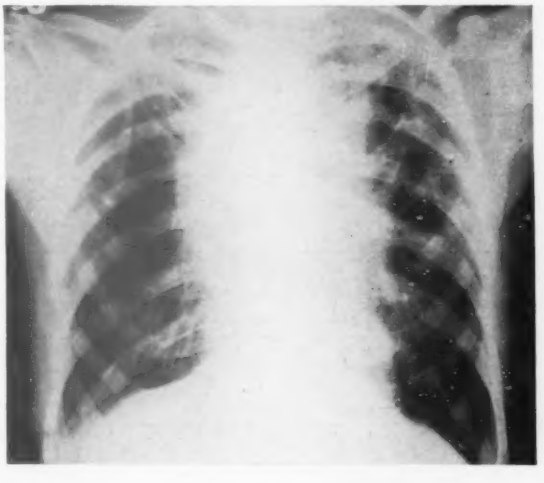

Fig. 12. Case xiii. Marked fibrosis in the medial portions of the lungs.

TABLE XIV

Year	Month	Field		Dose	Kv.	Ma.	Filter	Dist.
1927	5/16	R. axilla		600 r	200	30	0.5 mm. Cu	50 cm.
I	5/17	R. axilla, gold seeds implanted		460 mc-hr.				
	5/19–5/23	R. chest, lower; R. chest, lat.		600 r each	140	4	4 mm. Al	30 cm.
		R. supraclavicular		600 r	200	30	0.5 mm. Cu	50 cm.
1927	8/2–8/5	R. supraclavicular; R. axilla		600 r each	200	30	0.5 mm. Cu	50 cm.
II		R. chest, lat.		600 r	140	4	4 mm. Al	30 cm.
1928	1/23–4/3	8 treatments, rotating fields						
III		R. chest, lower—2 treatments	total	1300 r	140	4	4 mm. Al	30 cm.
		R. chest, lat.—2 treatments	total	1300 r	140	4	4 mm. Al	30 cm.
		R. breast—2 treatments	total	1100 r	200	30	0.5 mm. Cu	50 cm.
		R. axilla—2 treatments	total	1100 r	200	30	0.5 mm. Cu	50 cm.
1928	7/30–8/6							
IV		R. chest, post.; R. supraclavicular; R. axilla, direct		500 r each	185	30	0.5 mm. Cu	50 cm.
1928	12/13							
V		R. axilla, post.; R. supraclavicular, post.		500 r each	185	30	0.5 mm. Cu	50 cm.

presented marked telangiectasia and induration. Absorptive changes were present in the right scapula and upper ribs. The patient died on February 18, 1938. She represents a long-standing case of pneumonitis who developed metastases in the affected side eight years later.

CASE XV (Montefiore Hospital No. 27640). G. R., male, aged sixty-three (Table XV).

Status on Admission, November 9, 1939. Carcinoma of the lower and middle third of the esophagus.

Treatment. Two to three fields treated daily with doses of 250–400 r per field. Esophagoscopy following first and third courses showed presence of an epithelitis.

Course. Dysphagia and pain in dorsal area appeared two months following the last course of irradiation. Roentgenograms showed increased hilar markings, slight fibrosis of adjacent right lung and a few infiltrations at the right base. Gastrostomy performed. Films over the next seven months showed a dense infiltration in the medial portion of the right lung, increase in the infiltrations at the right base, elevation of the right diaphragm, left pleural effusion and suggestive pericardial effusion. During this period, the patient developed marked dyspnea, clubbing of the fingers and râles at both bases. Bronzing and atrophy of the treated skin was present. The patient died nine and a half months following the last irradiation.

Postmortem Examination. Carcinoma of the esophagus with extension to the pleura and contiguous structures, but not to the lung. Marked fibrosis and thickening of the pleura. Extreme fibrosis and atelectasis, with areas of acute inflammation and bronchiectasis, in the medial portions of the lungs. Small effusion in the pericardium. Moderate hypertrophy and dilatation of the right auricle and ventricle.

TABLE XV

Year	Month	Field	Size	Dose	Kv.	Ma.	Filter	Dist.
1936	11/16–11/23	Ant. and post. mediastinum	12×8 cm.	1600 r each	200	30	0.5 mm. Ag plus 1 mm. Al	70 cm.
I		R. ant. medial lung	12×8 cm.	750 r				
		L. ant. medial lung	12×8 cm.	500 r				
1936	12/7–12/12	Ant. and post. mediastinum	12×8 cm.	1500 r each	200	30	0.5 mm. Ag plus 1 mm. Al	70 cm.
II		R. ant. medial lung	12×8 cm.	400 r				
		L. ant. medial lung	12×8 cm.	550 r				
1936–1937	12/29–1/4	Ant. and post. mediastinum	12×8 cm.	1525 r each	200	30	0.5 mm. Ag plus 1 mm. Al	70 cm.
III		R. ant. medial lung	12×8 cm.	550 r				
		L. ant. medial lung	12×8 cm.	650 r				
		R. post. lung	12×8 cm.	400 r				

Case xvi (Montefiore Hospital No. 23973). L. K., male, aged fifty-two (Table xvi).

Status on Admission, September 19, 1933. Carcinoma of the lower third of the esophagus. Gastrostomy June, 1933.

Treatment. First course given elsewhere, 200 r per treatment. At Montefiore Hospital, second course, daily dose 330 r, third and and fourth courses, 250–300 r.

Course. Following the second course of irradiation, the esophageal obstruction disappeared. Third and fourth courses of irradiation were given for recurring esophageal obstruction. Roentgenograms, six weeks following Course III, showed a partial consolidation of the right lower lobe, a few infiltrations at the left base and slight elevation of the right diaphragm. Severe cough appeared three weeks after the last irradiation. Roentgenograms now showed fluid at both bases. One month later, there was atelectasis of both lower lobes with a few infiltrations at the bases and an increase in the right pleural effusion. The patient declined rapidly and died on February 2, 1935, ten weeks following the last irradiation.

Postmortem Examination. Fixation and stenosis of the esophagus but no evidence of carcinoma. Large bilateral pleural effusions. Marked fibrosis and atelectasis of the lungs. Stroma filled with lymphocytes, macrophages and multinucleated giant cells. Vessels are thickened, edematous and almost all plugged with thrombotic masses. Some are partially organized. Bronchi are dilated. Heart presents a small hemorrhagic pericardial effusion, a thick white external pericarditis with adhesions to the pleura, and adhesion of the anterior surface to the pericardium.

Fig. 13. Case xvi. Adhesive pericarditis (without cardiac enlargement as shown at postmortem). Atelectasis and fibrosis of right lower lobe, with some fibrosis of left lower lobe.

Case xvii (Montefiore Hospital No. 28032). S. S., female, aged sixty-two (Table xvii).

Status on Admission, October 22, 1928. Postoperative carcinoma of the right breast referred for prophylactic irradiation.

Treatment. Average dose 330 r.

Course. Following the second course of irradiation, which was given to a recurrence in the right axilla, the patient became very susceptible to upper respiratory infections. Roentgenograms six months later showed slight atelectasis and haziness of the right lung and a few atypical infiltrations in the right upper lobe. The third, fourth and fifth courses of irradia-

Table XVI

Year	Month	Field	Size	Dose	Kv.	Ma.	Filter	Dist.
1933 I	May	Ant. and post. mediastinum	10×15 cm.	1600 r each	200	5	0.5 mm. Cu plus 1 mm. Al	50 cm.
1933– 1934 II	10/27– 1/6	Ant. and post. mediastinum R. ant. and post. chest L. ant. and post. chest	12×8 cm. 12×8 cm. 12×8 cm.	2650 r each 2650 r each 2650 r each	200	30	0.5 mm. Ag plus 1 mm. Al	50 cm.
1934 III	3/29–	Same fields as in Course II	12×8 cm.	2000 r each	200	30	0.5 mm. Ag plus 1 mm. Al	50 cm.
1934 IV	9/17– 11/23	L. ant. and post. chest R. ant. chest Post. mediastinum R. and L. lat. chest	12×8 cm. 12×8 cm. 12×8 cm. 10×15 cm.	2000 r each 2000 r 2000 r 2000 r each	200	30	0.5 mm. Ag plus 1 mm. Al	50 cm.

TABLE XVII

Year	Month	Field	Size	Dose	Kv.	Ma.	Filter	Dist.
1928 I	10/22– 11/12	R. ant. chest R. ant. and post. supraclavicular R. ant. axilla		985 r 985 r each 850 r	200	4	0.5 mm. Cu plus 1 mm. Al	40 cm.
1929 II	9/24– 10/15	R. direct axilla R. ant. axilla R. post. axilla R. ant. chest and axilla	12×9 cm. 14×10 cm. 13×8 cm. 14×20 cm.	2270 r 1650 r 330 r 650 r	200	30	0.5 mm. Ag plus 1 mm. Al	50 cm.
1930 III	4/24– 5/9	R. ant. chest R. post. chest R. lat. chest	20×15 cm. 20×15 cm. 20×10 cm.	1025 r 955 r 985 r	200	30	0.5 mm. Ag plus 1 mm. Al	50 cm.
1930 IV	12/11– 12/31	R. ant. chest R. post. chest	16×24 cm. 15×22 cm.	985 r 750 r	200	30	0.5 mm. Ag 1 mm. Al	50 cm.
1931 V	3/4– 6/17	R. ant. chest R. post. chest R. upper and lower post. chest R. lat. chest	17×20 cm. 20×18 cm. 17×19 cm. 17×12 cm.	2300 r 1315 r 1315 r each 2300 r	200	30	0.5 mm. Ag plus 1 mm. Al	50 cm.

tion were given because irradiation changes in the right lung were interpretated as metastases. Dyspnea, cough, pain and cyanosis were severe following the fourth course. The right lung showed progressive atelectasis, increased infiltrations and marked thickening of the pleura. The right thorax became markedly contracted and in 1932 a dense shadow replaced the right lung. The skin was now severely telangiectatic and there was also a woodeny infiltration of the right chest wall. Following Course V, fractures were observed in the right 2nd, 3rd and 7th anterior ribs, and in the 6th and 9th posterior ribs.

FIG. 14. Case XVII. Marked contraction of right chest. Right lung replaced by a very dense shadow. Third and 7th right anterior ribs and 6th and 9th posterior ribs show healed fractures.

The fractures subsequently united. Over a period of years, the liver increased enormously in size with no clinical evidence of metastases. She died in August, 1938, with symptoms of right heart failure.

CASE XVIII (Montefiore Hospital No. 23187). F. R., female, aged forty-five (Table XVIII).

Status on Admission, October 18, 1933. Postoperative carcinoma of right breast.

Treatment. Irradiation, with the exception of the last course, was given at another institution. Dosage was massive. Course I was preoperative, Course II postoperative. Courses III and IV were given for "pulmonary metastases," diagnosed instead of pneumonitis. The average dose in the last course was 250 r.

Course. Chest pain and dyspnea began immediately after operation, November 4, 1932. By 1933, she already complained of orthopnea, weakness and night sweats. The lungs had been clear in 1932. A roentgenogram on March 2, 1933, showed on the right, pulmonic haziness with scattered soft infiltrations, especially in the medial portion, interlobar effusion and elevation of the dome of the diaphragm. By October, 1933, extensive fibrosis of the right lung and very thick right pleura were noted. In 1937, in addition, the trachea and mediastinum were markedly drawn to the right. The ribs on the treated side showed sharply delimited osteoporosis, irregularity of outline, and narrowing. The treated skin was telangiectatic and very indurated. Both lung and rib changes were sharply delimited and appeared directly be-

neath the telangiectatic skin areas. The symptoms of pneumonitis developed soon after operation, and the single massive doses, rather than the total dosage, must be considered the cause. With further irradiation, the right arm and axilla became painful. Cough and dyspnea progressed. In the later stages of this patient's illness, chills, fever and hemoptysis were prominent. The picture of right heart failure preceded death on June 2, 1938.

Postmortem Examination. The right lung was about one-half normal size, the trachea adherent to the upper lobe and the pleura hard, gray and about 1 cm. thick. On section, the lung was fibrotic and the bronchi dilated. A thrombus was present in the inferior pulmonary artery. The left lung was voluminous. The heart showed a small pericardial effusion, a slightly hypertrophied right ventricle and dilatation of the pulmonic conus. The left heart was negative.

The microscopic examination showed, in the right lung, a hyalinizing fibrosis with lymphocytic infiltration, dilated bronchioles and occasional lung abscess formation. Congestion and edema were present in the left lung.

The postmortem examination was negative for recurrence or metastases.

Fig. 15. Case xviii. Extensive fibrosis of the right lung with marked thickening of the pleura. Right thorax is very contracted. Right ribs are narrowed, irregular in outline and show areas of osteoporosis and sclerosis.

Roentgen Findings

Roentgen studies of the lungs in these patients, in the early stages of pulmonary reaction, reveal varying pictures of inflammatory changes. A common finding, at this time, is a haziness of the irradiated portion. This is soon followed by irregular patches of consolidation radiating out from the hilum. They are of uneven density and frequently coalesce. Such changes may manifest themselves after a few massive treatments or after a single intensive course of irradiation over fields of moderate size. When the irradiated fields are large, concomitant pulmonary and pleural reactions are the rule. In addition to the pulmonary consolidations above described, there are observed adhesions between the pleura and pericardium, and between the diaphragm

Table XVIII

Year	Month	Field	Dose	Kv.	Ma.	Filter	Dist.
1932	11/1	R. breast ant., lower half; R. breast lat.	700 r each	198	30	0.5 mm. Cu	50 cm.
I	11/2	R. breast ant.; upper half, R. axilla	700 r each	198	30	0.5 mm. Cu	50 cm.
1933	1/21–	R. breast ant., lower half; R. breast lat.	530 r each	140	4	4 mm. Al	30 cm.
II	1/23						
	1/26	R. breast ant., upper half, R. axilla	750 r each	198	30	0.5 mm. Cu	50 cm.
1933	3/2–	R. chest ant., upper half; R. chest post., upper half	800 r each	198	30	0.5 mm. Cu	50 cm.
III	3/6	R. chest ant., lower half; R. chest post., lower half	800 r each	198	30	0.5 mm. Cu	50 cm.
1933–	11/6–	R. chest ant., lower	1000 r total	200	30	2 mm. Cu	50 cm.
1934	1/10	R. chest post., lower	1250 r total			plus	
IV		Ant. mediastinum	750 r total			1 mm. Al	

and pericardium or pleura, with tenting of the medial portion of the diaphragm. Pleural, pericardial and, less frequently, interlobar effusions are occasionally present. If no further treatment is given, and if the initial course has not produced extensive injury, the sole residue months later may be slight pulmonary fibrosis and a few pleural, pericardial and diaphragmatic adhesions.

The late stages of severe lung damage are dominated by a picture of fibrosis. The normal architecture of the lung may disappear. Atelectasis is common in the area of irradiation, with compensatory emphysema in the non-involved portions. The diaphragm, in many instances, shows numerous pleural and pericardial adhesions, resulting in tenting and some elevation. The heart and trachea are drawn over to the involved side. Pleural thickening occasionally is marked and, at times, will obscure lung markings. The thorax, as a rule, becomes markedly contracted. With the passage of years, in addition to the fibrosis, fairly large and sharply outlined calcific plaques may appear in the irradiated lung or pleura.

SKIN CHANGES

As one would expect, patients with lung damage of any extent, all show damage to the overlying skin. In a mild case, the late changes consist of some telangiectasia and slight atrophy. In more severe cases, atrophy and telangiectasia are marked and, in addition, brawny induration is a constant feature. At times, the skin induration and resultant contraction of the chest wall are striking. Where the axilla and supraclavicular region are severely involved, the underlying tissues may reach a stage of stony hardness so that it interferes with drainage.

Comparison of the roentgenograms and the photographs of the skin shows that the area of pulmonary involvement corresponds to the area of skin damage.

BONE CHANGES

In some instances, when the total dosage is high, bone changes may be observed in the field of irradiation. These occur in patients surviving for long periods after treatment is given. Such changes manifest themselves as a rarefying osteitis. In the affected ribs are noted osteoporosis, sharply circumscribed circular areas of absorption, narrowing of the ribs and irregularity of contour. Fractures, in the absence of trauma, are common in the irradiated ribs or clavicle. Such fractures frequently will not unite. In time, eburnation of the ununited ends may take place, resulting in a type of pseudarthrosis. Where the bone displacement is slight, healing may be by bony union.

CLINICAL COURSE

Symptoms may present themselves before the pulmonary damage can be demonstrated by roentgen examination. The earliest signs are cough, usually non-productive and at times paroxysmal, slight dyspnea, and chest pain at the site of treatment. Fever and sweating may also occur. Where the damage is limited, these symptoms disappear following resolution of the pneumonitis.

Where the lung damage has been so extensive and severe that a permanent marked fibrosis is the result, the cough is persistent, the dyspnea progressive and especially marked on the least exertion, and the chest pain severe. Repeated upper respiratory infections, associated with chills, fever, heightened dyspnea and hemoptysis or streaking of the sputum, are also features of this stage.

After a varied period, which sometimes may last years, these severe cases go on progressively to a terminal stage. The symptoms now are predominantly those of right heart failure, including cyanosis, orthopnea, clubbing of the fingers, râles at the lung bases and, occasionally, an enlarged tender liver.

PATHOLOGY

Eight of the 11 patients who died had postmortem examinations. These were done six weeks to eight years following the onset

of the irradiation. The histological changes check very closely with those obtained in animal experiments.

Macroscopically, the irradiated portions of the lungs were atelectatic, firm in consistency and cut with increased resistance. The cut surfaces, at times, showed obliteration of normal lung markings. Injection of the pleura, fibrinous deposits, and extreme thickening, up to 1 cm., were observed. Occasionally, the lungs were adherent to the mediastinum and to the chest walls. In one patient, the two main pulmonary veins were almost completely occluded by granulation tissue. Another showed the trachea, bronchi and aorta matted together by fibrinous tissue.

Microscopically, inflammatory changes were found in the lungs and pleura. Where the irradiation was of long duration, severe fibrosis and hyalinization were present. In these patients, dilatation of the bronchi, bronchiectasis and bronchitis were also noted. Persisting alveoli were small and frequently filled with inflammatory exudate. Areas of edema, hemorrhage and necrosis were observed in the acute cases. Atherosclerosis of the pulmonary arteries, thickening, edema and thrombosis of the pulmonary vessels, and thrombosis of the inferior pulmonary artery were also present.

Changes in the heart were striking. Hypertrophy, or dilatation of the right side, was present in 6 cases; the 2 cases that did not show this finding ran an acute course and died one to two months following the appearance of pneumonitis. In no case was there enlargement of the left heart. Pericarditis and parietal pericardial adhesions were observed in 4 instances. Four patients also showed small associated pericardial effusions. Perivascular fibrosis of the heart vessels was found on one occasion.

MECHANISM OF RIGHT HEART FAILURE

As stated previously, the terminal picture of many of these patients with extensive radiation fibrosis, is one of right heart failure. The mechanism of this type of cardiac impairment is of considerable interest. It has been described in comparable lung conditions where marked infiltration of lung, bronchi and pleura serve to interfere seriously with the pulmonary circulation as, for example, in chronic pulmonary tuberculosis, of the fibroid type, and also in emphysema heart. As the fibrosis progresses, the capillary beds of the lungs become narrowed, and increased resistance results, i.e., hypertension of the pulmonic or lesser circulation. Enlargement and hypertrophy of the right heart then follow.

In these conditions, as in the postmortem findings previously cited, coronary artery disease was not seen. The exceptional pleural thickening, which was present in several of our patients, may have acted as a contributory factor. In those cases where the mediastinum was the seat of a dense fibrotic process, which surrounded bronchi, trachea and aorta, and even constricted the pulmonary veins, a direct interference with pulmonary circulation can be inferred.

With the establishment of pulmonary hypertension, there follows the train of compensatory events which is the basis for the clinical picture. These sequelae are increased venous pressure in the pulmonic circulation, marked lung congestion leading to hemoptysis, enlarged right heart and dilatation of the pulmonic conus, accentuation of the pulmonic sounds, enlargement of the liver, cyanosis and finally infarction of the lungs.

The right heart enlargement, observed at postmortem, was not easily discernible on the roentgenograms. Many of these cases originally had masses extending along the mediastinum and hilum or later, following irradiation, developed extensive hilar fibrosis, pericarditis and adhesions, and cardiac displacement. These changes alter the cardiac outlines markedly and make finer interpretation dubious.

While electrocardiograms exist for some of our patients, none were taken prior to irradiation, and the findings available are varied. It is hoped that in the future, reliable criteria can be assembled for such cases.

COMMENT

We do not possess, as yet, precise knowledge of the quantitative relationship of dosage to radiation pneumonitis. Therefore, no simple dosage formulas for lung irradiation can be offered, which will prevent its occurrence. Moreover, in treating thoracic malignant neoplasms, it is not always desirable to use dosages which will completely avoid this type of injury. First, because dosages must be applied which are bound to inflict some lung damage, if a real attempt to control the malignant condition is made; and second, because a limited degree of pneumonitis produces little in the way of symptoms or permanent functional impairment.

As was noted in the series of cases presented here, it is only severe radiation damage to a large portion of the lung and mediastinum which produces intolerable after-effects. The occurrence of severe injury should be borne in mind, so that treatment may be planned to avoid it. The following points, we believe, will prove of value in the prevention of major radiation damage:

1. The lung damage will appear under the portion of the chest wall that is most heavily irradiated and, where crossfire technique is used, in the region where the beams cross.

2. Massive doses, especially if repeated, and at close intervals, are likely to produce such injuries, even if the total dosage is not high, judged by today's standards. In these instances, it is not the total dosage which is the determining factor, but the amount given per treatment.

3. Irradiation which is limited to the lung periphery is less likely to produce serious injury than heavy irradiation over the mediastinum and large vessels.

4. Previous therapy, although no injury resulted with the earlier series, can be the basis for later damage, if subsequent treatment is not given with great caution.

5. If the primary therapy has resulted in some radiation pneumonitis, the likelihood of severe damage is great if additional therapy is given to such areas. The possibility is greater if large fields are used.

6. Where large fields are used, and marked skin changes occur, the possibility of such a lesion should be kept in mind and a careful watch kept for early signs.

7. Elderly individuals, with arteriosclerotic changes, must be considered more likely to have such damage.

8. Respiratory symptoms, such as cough, dyspnea and chest pain, are danger signals.

9. A diagnosis of pulmonary metastases must be accepted with reservation, when heavy dosage has been given, if based on changes found only in the part of the lung corresponding to the area of treatment.

10. Repeated roentgen studies of the lung during and following treatment will call attention to pulmonary damage in its incipient stages and will help differentiate this condition from metastases.

To conclude, the radiologist will find his best protection in avoiding lung damage, or at least limiting its extent, in the constant awareness of the conditions under which it occurs, and in the possibility of its occurrence in extensive irradiation over the thorax.

REFERENCES

1. BERGONIÉ, J., and TESSIER. Rapport sur l'action de rayons X sur la tuberculose. *Arch. d'électric. méd.*, 1898, *6*, 334–360.
2. DAVIS, K. S. Intrathoracic changes following x-ray treatment; clinical and experimental study. *Radiology*, 1924, *3*, 301–322.
3. DESJARDINS, A. U. Certain unusual features noted in a case of inoperable cancer of the breast treated by roentgen rays. *Med. Clin. North America*, 1923, *7*, 163–171.
4. DESJARDINS, A. U. The reaction of the pleura and lungs to roentgen rays. AM. J. ROENTGENOL. & RAD. THERAPY, 1926, *16*, 444–453.
5. DESJARDINS, A. U. Action of roentgen rays and radium on the heart and lungs. AM. J. ROENTGENOL. & RAD. THERAPY, 1932, Vols. 27 and 28.
6. DOWNS, E. E. Lung changes subsequent to irradiation in cancer of the breast. AM. J. ROENTGENOL. & RAD. THERAPY, 1936, *36*, 61–64.
7. ENGELSTAD, R. B. Experimental investigations of lung changes following röntgen radiation. *Acta radiol.*, 1933, *14*, 655–656.

8. Engelstad, R. B. Ueber die Wirkungen der Röntgenstrahlen auf die Lungen. *Acta radiol.*, suppl. 19, 1934, pp. 1–94.

9. Engelstad, R. B. Die Strahlenreaktion in dem Lungen beim Menschen. *Acta radiol.*, 1937, *18*, 32–43.

10. Evans, W. A., and Leucutia, T. Deep roentgen therapy of neoplastic pulmonary metastases. Am. J. Roentgenol. & Rad. Therapy, 1924, *11*, 35–50.

11. Evans, W. A., and Leucutia, T. Intrathoracic changes induced by heavy radiation. Am. J. Roentgenol. & Rad. Therapy, 1925, *13*, 203–220.

12. Flaskamp, W. *Sonderb. d. Strahlentherapie*, 1930, Vol. 12.

13. Groover, T. A., Christie, A. C., and Merritt, E. A. Observations on the use of copper filter in roentgen treatment of deep-seated malignancies. *South. M. J.*, 1922, *15*, 440–444.

14. Groover, T. A., Christie, A. C., and Merritt, E. A. Intrathoracic changes following roentgen treatment of breast carcinoma. Am. J. Roentgenol. & Rad. Therapy, 1923, *10*, 471–476.

15. Groover, T. A., Christie, A. C., Merritt, E. A., and Coe, F. O. Roentgen pleuropneumonitis. *South. M. J.*, 1927, *20*, 153–158.

16. Hartman, F. W., Bolliger, A., Doub, H. P., and Smith, F. J. Heart lesions produced by the deep x-ray; experimental and clinical study. *Bull. Johns Hopkins Hosp.*, 1927, *41*, 36–61.

17. Karlin, M. I., and Mogilnitzky, B. N. Zur Frage nach der Wirkung der Röntgenstrahlen auf die Lungen und das Herz der Tiere. *Frankfurt. Ztschr. f. Path.*, 1932, *43*, 434–447.

18. Küpferle, L. Experimentelle Studien zur Röntgenbehandlung der Lungentuberkulose. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1914, *21*, 85–89.

19. Küpferle, L., and Bacmeister. Experimentelle Grundlagen für die Behandlung der Lungentuberkulose mit Röntgenstrahlen. *Deutsche med. Wchnschr.*, 1916, *42*, 96–99.

20. Lüdin, M., and Werthemann, A. Lungenveränderungen nach experimenteller Röntgenbestrahlung. *Strahlentherapie*, 1930, *38*, 684–701.

21. McIntosh, H. C. Changes in lungs and pleura following roentgen treatment of cancer of the breast by prolonged fractional method. *Radiology*, 1934, *23*, 558–566.

22. Quadrone, C. *Zentralbl. f. inn. Med.*, 1905, *26*, 763.

23. Rudis-Jicinski, J. Electrochemical action of x-rays in tuberculosis. *New York M. J.*, 1901, *73*, 364–367.

24. Strasser, Alois, Pleuritis nach Röntgenbehandlung eines Mediastinal Tumors. *Ztschr. f. phys. u. diätet. Therap.*, 1912, *16*, 65–70.

25. Tsuzuki, M. Experimental studies of the biological action of hard roentgen rays. Am. J. Roentgenol. & Rad. Therapy, 1926, *16*, 134–150.

26. Tyler, A. F., and Blackman, J. R. Effect of heavy radiation on the pleura and lungs. *J. Radiol.*, 1922, *3*, 469–475.

27. Warren, S. L., and Whipple, G. H. Roentgen-ray intoxication. I. Unit dose over thorax negative—over abdomen lethal. Epithelium of small intestine sensitive to x-rays. *J. Exper. Med.*, 1922, *35*, 187–202.

28. Warthin, A. S., and Pohle, E. A. Effect of roentgen rays on the heart. *Arch. Int. Med.*, 1929, *43*, 15–34.

29. Wintz, H. Röntgenschädigungen in der Tiefentherapie. *Forschr. a. d. Geb. d. Röntgenstrahlen*, 1922, *30* (Kong. Heft), 133–138.

30. Wintz, H. Injuries from roentgen rays in deep therapy. Am. J. Roentgenol. & Rad. Therapy, 1923, *10*, 140–147.

31. Wintz, H. Erfahrungen in der Röntgenbehandlung des Karzinoms. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1926, *34*, 373.

32. Wohlauer, F. Der Einfluss der Röntgenstrahlen auf das Lungengewebe. *Deutsche med. Wchnschr.*, 1909, *35*, 1704–1706.

33. Zwerg, H. G. Die theoretischen, experimentellen, klinischen und wirtschaftlichen Grundlagen der protrahiert-fraktionierten Röntgenbestrahlung maligner Tumoren. *Strahlentherapie*, 1932, *43*, 201–248.

THE EFFECT OF VISIBLE LIGHT ON THE DEVELOPMENT OF TUMORS INDUCED BY BENZPYRENE IN THE SKIN OF MICE*

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INTRODUCTION

CONFLICTING results on effects of light on the skin of mice painted with benzpyrene are to be found in the literature. Doniach and Mottram[2] report that certain carcinogenic agents, including benzpyrene, sensitize the skin of animals to visible light. On the other hand, Taussig, Cooper and Seelig[5] could report no very significant difference between painted mice kept in the dark, and those exposed daily for one hour to an electric sun lamp.

Clark,[1] in a recent review, has suggested the possibility of a double action of radiation on the skin—one a sensitization to visible light, and also a carcinogenic effect of ultraviolet radiation, roentgen rays and radium. The preliminary experiments reported here were undertaken to investigate the effects of benzpyrene on mice kept throughout the experiment in an environment of (*a*) complete darkness, (*b*) twelve hour daily exposure to visible radiation.

EXPERIMENTAL PROCEDURE

The mice were kept in rooms, the construction of which has been fully described by Jones and Tuttle.[3] Forty mice of the Swiss Albino, Bar Harbour strain, were kept in Room I (complete darkness) and 40 in Room III (visible radiation). The mice were five to six months old at the beginning of the experiment. They were fed purina dog chow and distilled water; males and females were represented equally in each group, and segregated to prevent breeding.

Fluorescent lamps were substituted in Room III for the 1,500 watt tungsten lamps used before. Two types of lamps† were used, the "daylight" and the "blue" of the General Electric Company, both of them the 36 inch, 30 watt type. They were fitted, one blue and one daylight alternating, at the base of the duct and operated for twelve hours daily at a distance of 4 inches above each cage—a total of 20 lamps was used. The illumination, on the working plane, was 300 foot-candles at the start; this dropped, at the end of six months, to 200 foot-candles with aging of the lamps. The total energy was of the order of 0.1 gm/cal/cm²/min. of which about 10 per cent is in the far infra-red and about 5 per cent of wave lengths between 3,600 Å and 4,000 Å. We used the extra blue lamps because benzpyrene absorbs strongly in the blue region. The therapeutic and carcinogenic range of ultraviolet radiation was not present in the sources used.

The mice were painted twice weekly, in the interscapular region with 0.5 per cent solution of 3;4 benzpyrene in benzene and without previous epilation. A No. 8 camel's hair brush was used. A total of 35 paintings was given over a period of seventeen weeks. The mice were observed for sixty days after this. The experiment lasted from May 10 to November 10, 1939.

RESULTS

The results are given in Table I.

We observed a marked difference in the reaction of the mice in the two rooms to the first few paintings. After only 4 paintings 93 per cent of the total in the light room showed definite bald patches, while only 59 per cent of those in the dark room showed any sign of baldness. The animals in the light room tended to stay bald, appeared to lose weight and showed a more marked constitutional reaction to the carcinogen at the start.

The means with their standard errors show no significant difference in the length of the latent interval to the development of the first papilloma between the two groups.

† The spectral characteristics of these lamps has been described by G. E. Inman in "Characteristics of Fluorescent Lamps." *Tr. Ill. Eng. Soc.*, 1939, *34*, 65.

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It was observed, however, that in 6 cases of the group in the light, papillomata disappeared; in no case did this happen in the dark room group. A significant lengthening is seen in the light room group, of the latent interval to the development of the first carcinoma, also a significant lengthening of the interval from papilloma to carcinoma. The incidence of cancer, by pathological diagnosis, was 79 per cent in the dark room, and only 44 per cent in the light room groups. Taken together, these results indicate a retardation of the carcinogenic process, as well as a diminution in the number of animals affected, in the group exposed to light. The animals in the light room group that did not develop tumors were killed at the same time as the others and appeared healthy at autopsy.

TABLE I

EFFECT OF LIGHT AND DARKNESS ON THE DEVELOPMENT OF SKIN TUMORS BY 3;4 BENZPYRENE

	Et	Papillomata				Carcinomata					Ca per cent
		No. mice with	Total No.	No. per mouse	Latent interval to 1st	No. mice with	Total No.	No. per mouse	Latent interval to 1st	Interval from 1st pap-ca.	
Room I, dark	38	37	111	2.9	111 ±4.7 days*	30	58	1.5	144 ±4.7 days	35 ±3.2 days	79
Room III, light	34	29	72	2.1	121 ±5.2 days	15	28	0.8	168 ±4.3 days	56 ±7.3 days	44

Et = Effective total, number of mice that did not die before the appearance of the first papilloma.
* This and all following errors = standard errors.

The tumors found on microscopic examination of tissue were mostly of the squamous cell carcinoma type. In 2 cases, one in each room, a fibrosarcoma was found. One lung adenoma was found (dark room group) and one mediastinal lymphoma (light room group). The spleens in most cases were enlarged and showed hyperplasia and congestion; in 2 cases, one in each room, marked hyaline degeneration.

DISCUSSION OF RESULTS

Recent work of Rusch, Baumann and Kline[4] on tumors, produced by intense ultraviolet irradiation, on the ears of mice, shows that the production of such tumors can be accelerated by local applications of certain oils. The most effective were mineral oil and cholesterol in oil. But these authors found, in agreement with the results on benzpyrene of Taussig, Cooper and Seelig,[5] no effect of ultraviolet light on the activity of a carcinogen, 1;2;5;6 di-benzanthracene. Our results indicate that radiations in visible light, from which ultraviolet radiations have been excluded, have some influence on the carcinogenic action of benzpyrene. It was, however, evident to us that in the early stages of the experiment the "light room" group were showing constitutional changes at a time when the "dark room" group showed very little reaction to the carcinogen. Since, in the opinion of some workers, more tumors will occur in healthy stock than in stock physically below par, the higher percentage of tumors in our mice deprived of light can possibly be explained as tumors developing in a better nourished animal. If this difference in nutrition were not a factor, we might suspect either that radiation had changed the carcinogenic activity of benzpyrene, or else, by sensitizing the skin, produced a more resistant medium. If the latter were true it would seem that the effect of radiation in visible light may differ from known carcinogenic effects of ultraviolet.

The matter is being investigated further using mice of other strains.

CONCLUSIONS

Two groups of mice, of the Swiss Albino strain, were painted twice a week with 3;4 benzpyrene for seventeen weeks to induce skin tumors. One group was kept, throughout the experiment, for twelve hours daily in an environment of visible light, the other in complete darkness. A retardation of the carcinogenic process, and a diminution in the number of animals which developed tumors was found in the group exposed to light. It is suggested that radiations in visible light may differ, in their effects on the skin, from known carcinogenic effects of ultraviolet.

We wish to thank Dr. G. B. Mider for kind collaboration and much valuable help during the conduct of the experiment. Our thanks are also due to Dr. Clifton Tuttle for supplying data on wave length limits of lamps, values for illumination, and energy equivalents of the radiations used.

REFERENCES

1. CLARK, J. H. Biological effects of radiation. *Ann. Rev. Physiol.*, 1939, *1*, 21–40.
2. DONIACH, I., and MOTTRAM, J. C. Sensitization of the skin of mice to light by carcinogenic agents. *Nature*, 1937, *140*, 588.
3. JONES, L. A., and TUTTLE, C. Isolation of desired qualities of radiant energy for biological experimentation *J. Nutrition*, 1939, *18*, 611.
4. RUSCH, H. P., BAUMANN, C. A., and KLINE, B. E. Effect of local applications on development of ultraviolet tumors. *Proc. Soc. Exper. Biol. & Med.*, 1939, *42*, 508.
5. TAUSSIG, J., COOPER, Z. K., and SEELIG, M. G. Effect of light on benzpyrene cancer in mice. *Surg., Gynec. & Obst.*, 1938, *66*, 989–993.

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FURTHER STUDIES ON THE ACTION OF ROENTGEN RAYS ON THE GAMETES OF *ARBACIA PUNCTULATA**

I. DELAY IN CELL DIVISION CAUSED BY EXPOSURE OF SPERM TO ROENTGEN RAYS

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IT HAS been shown previously[1,2,3,4] that (1) exposure of sperm or eggs (or both) of *Arbacia punctulata* to hard roentgen rays before fertilization causes a delay in the occurrence of the first cleavage, that (2) increased exposure causes increased delay, that (3) no delay is caused by comparable doses when cytoplasm alone is treated, and that (4) recovery from the effect may occur before fertilization when eggs are treated but not when sperm are treated. With the exception of point (3) these results have been repeated and confirmed by Miwa, Yamashita and Mori[5] using the related form *Pseudocentrotus depressus* and found to be true also when beta or gamma rays are used in place of roentgen rays.

It is the purpose of this report to examine more critically the relation between dose of radiation administered and the amount of delay in cell division observed and to analyze the nature of the reaction in the light of the more recent findings.

MATERIAL AND METHODS

For the present work sperm alone were treated. This was done in order that the complicating factor of recovery, which enters in when eggs are treated, might be avoided. Eggs and sperm were collected in the usual way and "dry sperm" (i.e. exuded sperm material not diluted with sea water) was exposed in amounts of one or two small drops in thin walled celluloid pill boxes.

The roentgen-ray equipment used was the dual-tube self-rectifying outfit available at the Marine Biological Laboratory, a simultaneous cross-firing technique thus being used. The secondary voltage was 194 kv. and the tube current on each tube was 25 ma. The output intensity (as measured in air with a celluloid thimble type ionization chamber) at the point of treatment and after the radiation had passed through the heavy glass of the tube walls and 5 mm. of bakelite of the tube shields (equivalent inherent filter: 0.2 mm. copper) was 7,800 roentgens per minute. The distance from the center of each target to the center of the test material was 9.5 cm.

The exposure times were 0 (controls), 1, 2, 4, 8, 16, 32 and 64 minutes, the timing being carried out and the conditions mentioned above being maintained as precisely as possible. At the end of each exposure, a portion of the treated sperm material was removed, diluted properly with sea water and allowed to fertilize normal eggs. The cleavage time—that is, the time intervening between the moment of insemination and the moment when some particular percentage had divided—was then carefully determined in accordance with procedures previously described. For the experiments reported here, the times when various percentages of cleavage occurred were recorded. Moreover, an attempt was made to note the time when the first cell divided in each sample and also the time when the first ten had divided. The times of the first and the first ten cleavages in the samples did not bear a precise relation to the times

* The work to be reported in this series of papers was carried out mainly at the Marine Biological Laboratory, Woods Hole, Mass. Part of it was done while the author was connected with the Memorial Hospital, New York City, and the remainder since transferring to the National Cancer Institute. The microscopical sections and part of the drawings used here were prepared by Mr. Joseph C. Bender whose services were provided by the Memorial Hospital. The author is indebted to the Memorial Hospital for support of the early part of the work and to the Marine Biological Laboratory for use of its excellent facilities.

when various percentages had cleaved since the number of individuals in the samples was not the same, but they did serve to indicate whether any of the individuals escaped irradiation effect entirely.

RESULTS

The results for a typical experiment are given in Table I and plotted in Figure 1, the first and second points on each curve (Fig. 1) indicating the time of the first and first ten cleavages in each case, respectively. It will be noted (1) that in accord with what has been described previously, there is a general delay in the occurrence of cleavage and that this becomes greater as the amount of treatment administered is increased; (2) that among the controls cleavage occurs in practically all of the cells at the same time as indicated by the steep slope—almost vertical character—of the curve; (3) that in the irradiated samples cleavage occurs less uniformly among the cells, as indicated by the decrease in steep-

TABLE I

Cleavage	Minutes' Cleavage Time							
	1st	10th	10%	30%	50%	70%	90%	98%
Min. Exposure								
0 (Control)	—	—	41	41½	42	42½	43	45
1	54	67	82	84	85	87	89	95
2	65	81	98	104	108	110	113	119
4	66	99	123	127	130	135	139	143
8	—	99	150	154	157	159	162	169
16	115	151	175	182	185	188	194	207
32	146	167	194	204	211	215	222	—
64	—	—	—	—	—	—	—	—

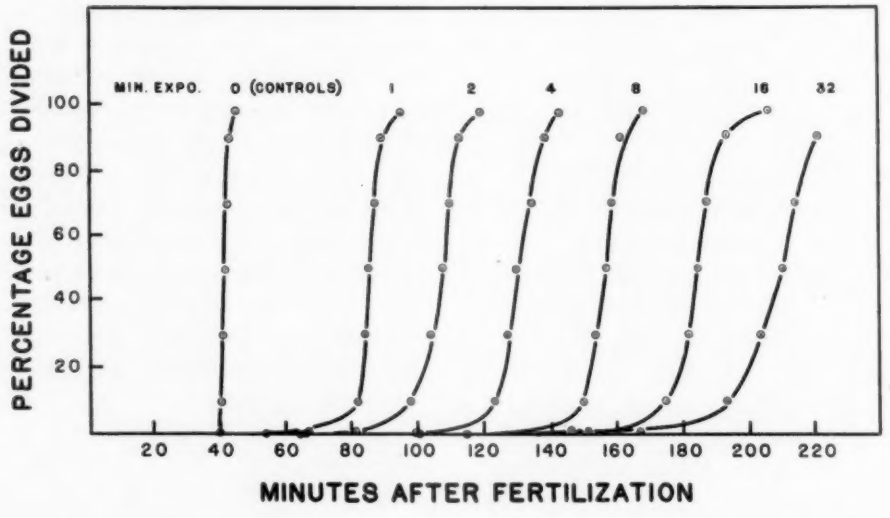

FIG. 1. Curves showing the percentage of eggs divided at various times after fertilization when different doses of roentgen rays are administered to the sperm before fertilization. (The first and second points in each case, however, are not based on percentage of eggs cleaved, but rather the times of the first and first ten cleavages, respectively.)

ness of the curves, but whereas a few of the cells cleave much earlier and some much later than the rest, most of them nevertheless divide at nearly the same time; (4) that none of the *functional* sperm fail to carry irradiation effect (as manifest by cleavage delay) into the eggs; and (5) that all of the eggs were successfully fertilized when the roentgen treatment did not exceed thirty-two minutes' exposure (250,000 r approximately).

In view of the fact that most of the eggs in a sample cleaved at about the same time, the moment of 50 per cent cleavage may be taken as most representative in each case. Such values as read from the curves (Fig. 1) are 42, 85, 108, 131, 157, 185 and 210 minutes, respectively, for samples receiving 0 (control), 1, 2, 4, 8, 16 and 32 minutes' exposure. Subtracting the value for the control from those for the irradiated samples to obtain the actual minutes' delay caused by the treatment, the following figures were obtained: 43, 66, 89, 115, 143 and 168. These are plotted in Figures 2 and 3 to show how the irradiation effect (delay in cleavage) varies with dose of radiation (dose-effect curves).

It will be seen (1) that the curve (Fig. 2) rises rapidly at first but tends to become

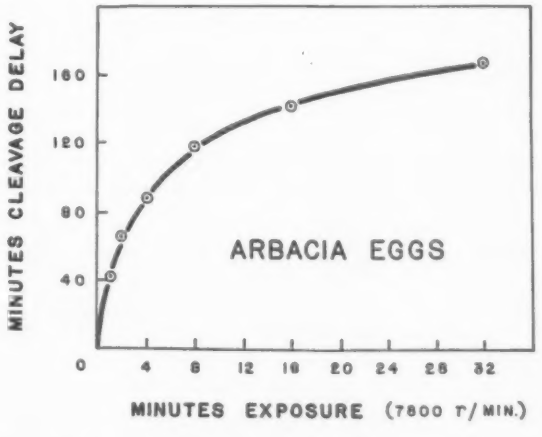

Fig. 2. Curve showing the minutes cleavage delay in fertilized *Arbacia* eggs whose sperm had received various exposures to roentgen rays before fertilization.

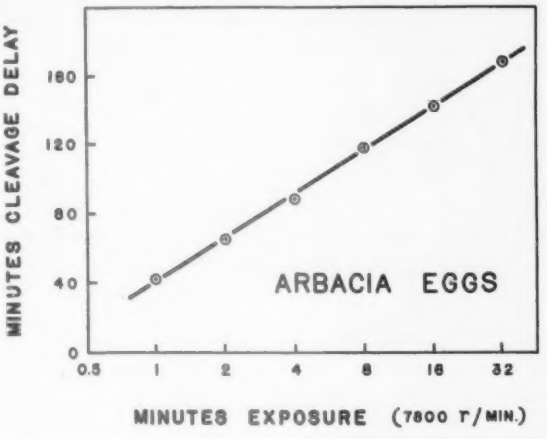

Fig. 3. Same as Figure 2, semi-logarithmic plot.

flattened, and (2) that a perceptible threshold effect is indicated only by the semi-logarithmic plot (Fig. 3). Thus the die-away character of the reaction suggests that something is being used up or destroyed by the radiation, and the close fitting of the experimental points to the exponential type of curve suggests that the reaction must be controlled by a single substance. The possible meaning of these suggestions will be dealt with further below.

Thus far only a single experiment has been described. However, after a variety of exploratory tests had been performed, ten experiments of the type described above were carried out on different days and on different collections of material under as nearly the same conditions as possible. Briefly, it may be said that the same kind of delay was observed in every case and that the same type of dose-effect curves were obtained, these varying only in slope. Figures 4 and 5 show the most extreme variations in slope observed.

DISCUSSION

It is instructive to compare the response of the sea urchin material to roentgen rays with that of the photographic plate to light (Table II).

Exposure of the photographic plate to light produces a latent image which be-

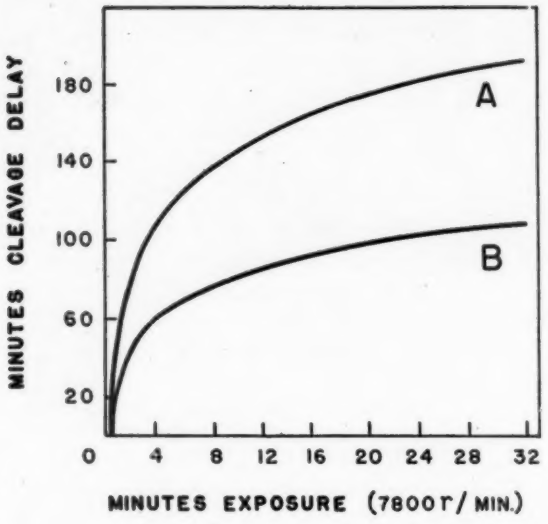

FIG. 4. Curves showing the minutes cleavage delay in fertilized eggs whose sperm had received various exposures to roentgen rays before fertilization. Curve *A* is for the most sensitive collection of material used, and Curve *B* for the most resistant.

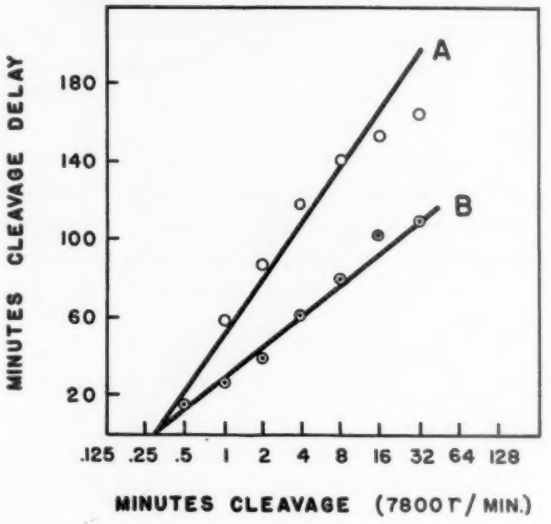

FIG. 5. Same as Figure 4 with experimental points shown—semi-logarithmic plot.

comes manifest only upon development (photographic), the intensity of which varies directly with the logarithm of exposure to light over the major portion of the range of the reaction (in particular cases) (Fig. 6). Similarly, exposure of the sea urchin gametes to roentgen radiation produces a latent effect which becomes manifest only upon fertilization and the amount of effect (cleavage delay) is found to vary directly with the logarithm of exposure to roentgen radiation over the greater range of the reaction.

In case of the photographic plate, it is known that light acts upon the photographic emulsion causing metallic silver to be deposited when the plate is developed, and

TABLE II

Points Compared	Sea Urchin Material	Photographic Plate
Treatment	Exposure to roentgen rays	Exposure to light
Unobserved result	Latent effect (delay)	Latent image
Demonstration of result	Fertilization and determination of cleavage time	Photographic development
Observed result	Delay in cell division	Photographic image
Degree of effect	Amount of delay varies directly with log dose	Density of plate likewise varies directly with log dose

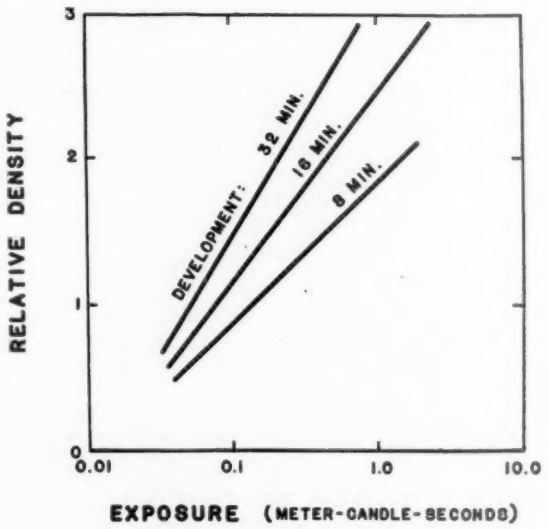

FIG. 6. Curves for 8, 16 and 32 minutes' development times, showing the relative density (degree of blackening) produced in a photographic plate for various exposures to light. (Data from Hardy and Perrin.)

further, that the density (the degree of blackening) is directly proportional to the amount of silver deposited per unit area of the plate. From this it is clear that the slope of the curve (Fig. 6) characterizes the rate at which silver is transformed by the light for any given development time. To what extent the response of the sea urchin gametes is like that of the photographic plate in these respects is not yet evident, but knowledge of the somewhat better understood photographic reaction has served to influence analysis of the gametic response.

By purely subjective reasoning, it is clear that in case of the living test objects the same as in case of the photographic plate, radiation acts on some substance (or substances), which for the sake of simplicity may be called (x), and that as (x) is used up or changed, certain photo-products (p) must be formed from (x). Moreover, from the work with non-nucleated egg fragments and the fact that cleavage delay may be caused by irradiating sperm alone, it appears that (x) is most likely a nuclear constituent. In case of the photographic plate, it is clear that darkening of the plate is caused by a photo-product (p)—that is, by silver being deposited, but in case of the gametes no evidence is yet available to indicate whether loss of (x) or the formation of (p) is responsible for the effect observed. The question at this point, therefore, becomes resolved into one of whether roentgen rays destroy a substance in the nucleus which acts under normal circumstances to keep the mitotic schedule "on time" or whether they cause a new substance (p) to be produced which acts to slow the mitotic schedule. Because of the complex nature of the living system, the loss of some essential substance seemed as likely to be responsible for the effect observed as the formation of some toxic photo-product. Although the findings were negative, it is of interest at this point to mention a search for evidence of (p).

In previous experiments dealing with the recovery phenomenon, it was observed that 80 to 90 per cent of the recovery which occurred took place within the first hour after treatment ceased. Further, it was observed that the curve showing loss of effect (recovery) as a function of time resembled the exponential type very closely. Considering the significance of these facts it seemed that the rate of recovery was too slow to be characteristic of the recombination of ions produced by the radiation and too fast to be characteristic of biological repair in the healing sense. The rate, however, did seem about right for the diffusion out or loss of a toxic photo-product such as (p) above, thus giving some reason for expecting that (p) might be demonstrated.

A heavy suspension of eggs with barely enough sea water to cover them was exposed to large doses of radiation (50,000 r). Following treatment the eggs were allowed to stand in the treated sea water for an hour, at the end of which time the supernatant fluid was removed and placed over fresh non-irradiated eggs. One hour later these eggs were fertilized and their cleavage time determined. It was expected that if (p) diffused out of the irradiated eggs into the sea water medium, it might in a similar manner diffuse back into the fresh eggs enough to cause a detectable delay. As intimated above, the results were entirely negative.*

While this finding is in line with the idea that photo-products are not important in causing the slowing of cell division, it really does not furnish proof to that effect. The experiment was of the type that positive results would have yielded significant evidence, whereas negative results could have little meaning. The experiment just described, therefore, proves only that the presence of (p) has not as yet been demonstrated. It is clear that if the egg membranes were semi-permeable to (p), allowing it to pass outward only, or that if (p) were changed chemically upon reaching the sea water, the experiment could not be expected to demonstrate (p). Thus, while instruc-

* That is, aside from a slight effect (1 to 2 per cent of the maximum obtainable effect) that could be obtained by treating sea water alone.

tive, the finding serves mainly as a guide for further work.

In addition to comparing the response of sea urchin material with that of the photographic plate, it is of interest to compare it with another which in some respects is more like that of the sea urchin. Redfield and Bright[7]* found that exposure of *Nereis limbata* eggs before fertilization to roentgen and beta rays caused an increased swelling

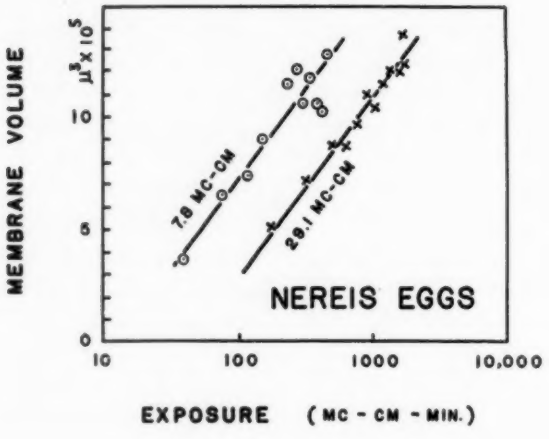

FIG. 7. Curves showing membrane volume in *Nereis* eggs after various exposures to beta rays. (Data from Redfield and Bright.)

of the fertilization membrane of the egg upon fertilization, and that the degree of swelling varied linearly with the logarithm of the dose of radiation administered (Fig. 7) for the major portion of the range of the reaction. Moreover, it was found that the reaction involved was limited to extranuclear components and that it was irreversible.[8] The authors pointed out in connection with their observations that the findings are consistent with the view that the physiological effects of the radiations are due to the ionization of some substance in the jelly material of the egg.

Thus, in both the *Arbacia* and *Nereis* materials radiation produces latent effects which become manifest only upon fertilization; the irradiation effect is irreversible in *Arbacia* sperm and *Nereis* eggs, but not so in *Arbacia* eggs; the significant change brought about appears to be produced in nuclear material in case of *Arbacia* and in extra-nuclear material in case of *Nereis;* and in both *Arbacia* and *Nereis* the effect appears to vary with the rate at which some particular protoplasmic material is used up or destroyed. It would seem, therefore, that while there are certain significant differences in some parts of the reactions, the general character of the mechanism involved may be quite similar in the two cases.

Investigation of the relation of absorbed energy and the size of certain morphological entities involved in the reaction provide further instructive information. From the definition of the roentgen, one such unit of radiation produces approximately 2.1×10^9 ion pairs per cubic centimeter of atmospheric air (the exact number being known very closely for standard conditions). Hence, assuming that the energy absorbed by any material is nearly proportional to its density, the number of ion pairs produced by one roentgen in 1 cc. of water or tissue is approximately 850 times that produced in air or 1.785×10^{12} ion pairs. Taking the dose of a threshold detectable effect as being in the neighborhood of 2,500 r (Fig. 3) and the size of the average complex molecule of the nucleus as being in the neighborhood of 40,000 cu. Å (Clark, p. 11),[9] then one ion pair is produced for every 5.6×10^3 molecules. Likewise, taking the size of the sperm as 100 cu. mu, around 4.46×10^7 ion pairs per sperm must be produced in order to bring about any appreciable delay in cleavage.

Similarly, taking 300,000 r as being a dose which produces close to the maximum effect (Fig. 3)† and the size of the average molecule as above, one ion pair is produced for every 46.7 molecules and 5.35×10^9 ion pairs per sperm are produced.

* And in previous papers.

† The round figure of 300,000 is taken from a region of the curve where it is becoming very flat. It is interesting in this connection to call attention to the fact (Table 1) that sixty-four minutes' exposure (approximately 500,000 r.) prevents all fertilization, and that in work unreported here, doses of 300,000 to 400,000 r were found adequate to prevent fertilization on the part of all but a few sperm in a sample.

These figures must be considered only approximate at best, but they do furnish some impression of the limits within which the changes must take place. It is clear, for example, that close to the maximum effect may be obtained with ionization occurring in only a small percentage of the molecules (a little over 2 per cent according to the figures), thus making it difficult to understand how any available sensitive substance could be used up to completion without as much as a one-to-one correspondence of ion pairs and sensitive molecules being reached—that is, unless some kind of multiplying mechanism is in effect. To obtain such a correspondence (on the basis of the above considerations) it would be necessary to show that around 50 times more ion pairs are produced than at present accounted for.

There are, of course, two rather uncertain factors used in the calculations—the exact size of the sensitive molecules and the precise amount of ionization produced in tissue per roentgen. It seems unlikely at this stage, however, that these could change enough as a result of future findings to account for the large discrepancy.

The developments, therefore, direct attention to three important questions: (1) whether a multiplying mechanism is not in some way effective—that is, whether a change produced in one molecule by ionization can be passed along to other molecules without the aid of further ionization; (2) whether large molecular aggregates may not be the sensitive units acted upon by the radiation to cause the effect observed; and (3) whether chemical change may be produced in a living system by radiation in significant amounts without ionization—that is, by excitation. It is hoped that future investigation will elucidate these points.

SUMMARY

1. Normal eggs of *Arbacia punctulata* were fertilized with sperm which had been exposed to various doses of hard roentgen rays and the time intervening between insemination and the first cleavage carefully determined.

2. The following were found: (1) that (as observed previously) the occurrence of the first cleavage was definitely delayed by the irradiation; (2) that for relatively small doses none of the sperm failed to carry irradiation effect into the eggs; (3) that the amount of delay varied linearly with the logarithm of exposure for the greater range of the effect produced; and (4) that fertilization was prevented entirely only after doses of 300,000 r or greater had been applied.

3. These results show that cell division, in this particular case, can be retarded by irradiation produced in one-half the normal nuclear component, and that the effect is clearly cumulative in each cell treated, thus demonstrating that the reaction is characteristically different from the all-or-none "hit" or target type.

4. The shape of the dose-effect curve suggests that the delay in cleavage varies with the rate at which some sensitive substrate is being changed or destroyed by the radiation.

5. Calculations, however, make it appear that the effects obtained cannot be attributed to ionization alone unless the sensitive units are large molecular aggregates.

REFERENCES

1. Henshaw, P. S. Studies of the effect of roentgen rays on the time of the first cleavage in some marine invertebrate eggs. I. Recovery from roentgen-ray effects in *Arbacia* eggs. Am. J. Roentgenol. & Rad. Therapy, 1932, *27*, 890–898.

2. Henshaw, P. S., Henshaw, C. T., and Francis, D. S. The effect of roentgen rays on the time of the first cleavage in marine invertebrate eggs. II. Differential recovery and its influence when different methods of exposure are used. *Radiology*, 1933, *21*, 533–541.

3. Henshaw, P. S., and Francis, D. S. The effect of x-rays on cleavage in Arbacia eggs; evidence of nuclear control of division rate. *Biol. Bull.*, 1936, *70*, 28–35.

4. Henshaw, P. S. The action of x-rays on nucleated and non-nucleated egg fragments. *Am. J. Cancer*, 1938, *33*, 258–264.

5. MIWA, M., YAMASHITA, H., and MORI, K. The action of ionising rays on sea-urchin. 1. The effects of roentgen, gamma and beta rays upon the unfertilized eggs and sperms. *Gann*, 1939, *33*, 1–12.
6. HARDY, A. C., and PERRIN, F. H. The Principles of Optics. McGraw-Hill Book Co., New York, 1932.
7. REDFIELD, A. C., and BRIGHT, E. M. The physiological action of ionizing radiations; evidence for ionization by β-radiation. *Am. J. Physiol.*, 1924, *68*, 54–61.
REDFIELD, A. C., and BRIGHT, E. M. The physiological action of ionizing radiations; path of α-particle. *Am. J. Physiol.*, 1924, *68*, 62–69.
REDFIELD, A. C., and BRIGHT, E. M. The physiological action of ionizing radiations; x-rays and their secondary corpuscular radiation. *Am. J. Physiol.*, 1924, *68*, 354–367.
8. REDFIELD, A. C., and BRIGHT E. M. The physiological changes produced by radium rays and ultra-violet light in the egg of Nereis. *J. Physiol.*, 1921, *55*, 61–85.
9. CLARK, A. J. The Mode of Action of Drugs on Cells. Williams & Wilkins Co., Baltimore, 1933.

Vol. 43, No. 6

FURTHER STUDIES ON THE ACTION OF ROENTGEN RAYS ON THE GAMETES OF *ARBACIA PUNCTULATA*

II. MODIFICATION OF THE MITOTIC TIME SCHEDULE IN THE EGGS BY EXPOSURE OF THE GAMETES TO ROENTGEN RAYS

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IN THE paper just preceding (and previously) it has been shown that irradiation of sperm or eggs (or both) of *Arbacia punctulata* with hard roentgen rays before fertilization causes a delay in the occurrence of the first cleavage. It is the purpose of this report to give account of an investigation to ascertain whether the whole cleavage cycle—that is, the whole time from the moment of fertilization until the egg has divided—is slowed uniformly or whether certain parts are slowed more than others. This is important since it is desirable to know whether the slowing is associated with the sperm when it exists as a separate entity or with the more strictly mitotic behavior of the egg.

The events which occur between fertilization and the first cleavage have been carefully described by Fry.[1] The developmental advance was noted by Fry in two ways: by observing the living material and by fixing samples at different stages which could be examined critically after sectioning and staining.

In the living egg, four stages are recognizable, due largely to various configurations of the aster and more transparent nucleus. Stage 1 displays a clear nuclear area having a diameter about one-tenth that of the whole egg (see photographs, Fig. 1, of unfertilized eggs and eggs five minutes after fertilization). Stage 2 shows a light crescent extending almost across the whole egg when viewed from the proper angle (Fig. 1, eggs fifteen minutes after fertilization). Stage 3 shows the enlarged prophase nucleus (visible in a good many of the photographs, Fig. 1—see particularly the one for normal material twenty-five minutes after fertilization). Finally, Stage 4 presents a dumbbell shaped clear area which can be seen for only a short time just prior to cleavage when viewed in the right plane (visible in only a few eggs, Fig. 1). As made clear by the photographs presented here, we have noted the same stages as observed by Fry.

From a study of fixed material, Fry describes the following events as occurring:

1. Entrance of the sperm head into the egg cytoplasm.
2. Elaboration of the sperm aster and movement of the sperm pronucleus toward the egg pronucleus.
3. Fusion of the pronuclei during which the identity of the sperm pronucleus becomes lost and the sperm aster becomes more prominent.
4. Formation of the crescent from the sperm aster and its later disappearance.
5. Prophase—marked by the appearance and growth of two new asters* and the formation of chromosomes.
6. Metaphase—the stage during which the chromosomes are aligned in the equatorial plate.
7. Anaphase—from the time when the chromosomes have separated until they begin to dissolve.
8. Telophase—the stage during which the chromosomes dissolve and the cell divides.

We likewise have observed these events and have prepared a mitotic time schedule (Fig. 2, upper part) patterned, for the most part, after the one developed by Fry.

* These originate close together and move to opposite poles of the egg.

Fry's observations were made on material kept at 20° C. whereas ours was kept at 25° C. While the higher temperature caused the cleavage cycle to progress more rapidly, the separate events appeared to occur at the same time with respect to each other. Thus, the figure as shown is mainly a reproduction of Fry's schedule without the actual time indicated, which does not concern us particularly here.

Our problem, as stated, but which can be indicated more specifically at this point, was to ascertain whether the various stages or events occurring in the cleavage cycle maintained the same time relationship to each other although the cleavage cycle itself was much prolonged by exposure of one of the gametes to roentgen rays.

Eggs and sperm were irradiated separately in thin walled celluloid pill boxes as described in the previous paper, an exposure of eight minutes (62,400 r) being given. This exposure was selected because it produces a large amount of delay and would thus tend to manifest more strongly any differential slowing which might be produced.

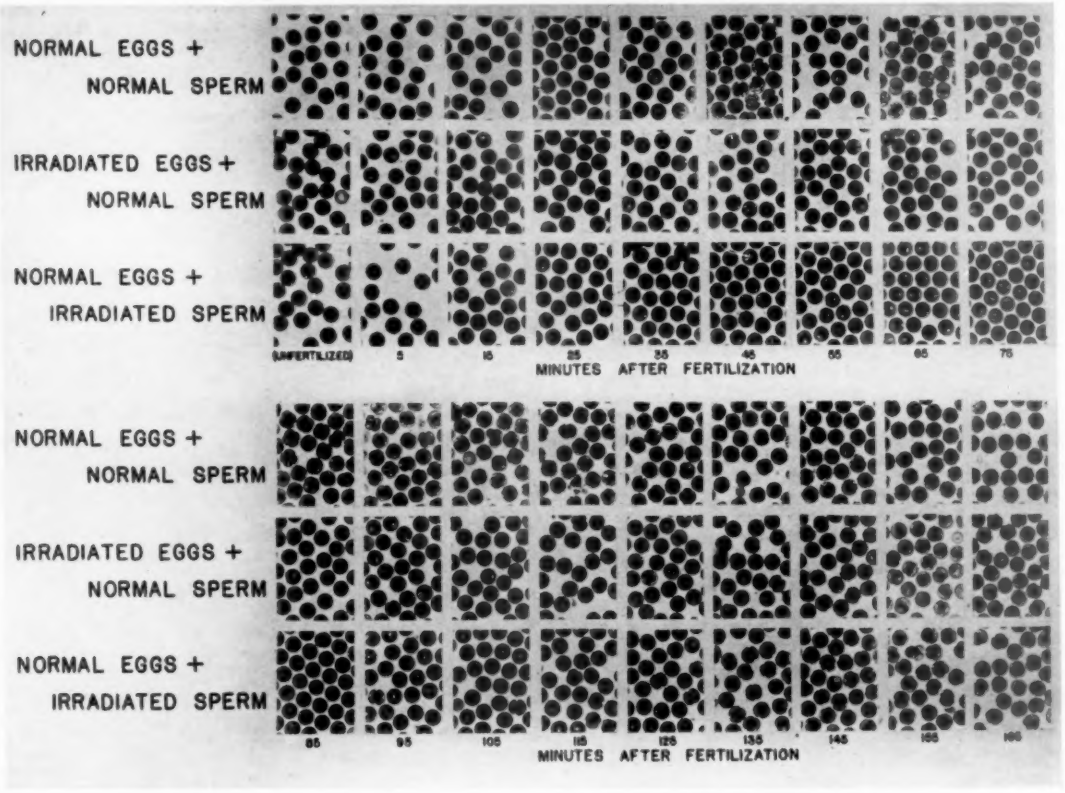

FIG. 1. Photomicrographs showing early development in *Arbacia* eggs. The first and fourth rows show normal development, the second and fifth show development after the eggs had received doses of 62,400 r of roentgen rays before fertilization, and the third and sixth show similar development after the sperm had received this dose.

After treatment three combinations of gametes were arranged:

(1) Normal Eggs (N.E.) + Normal Sperm (N.S.) (Control Series)

(2) Irradiated Eggs (I.E.) + Normal Sperm (N.S.)

(3) Normal Eggs (N.E.) + Irradiated Sperm (I.S.)

The three sets of material were then watched during the course of the first cleavage cycle. After running several such series and becoming familiar with the events which can be seen in the living egg,

it was decided (1) to make photographs of the three kinds of material at ten-minute intervals beginning five minutes after fertilization, and (2) to fix samples at various stages for subsequent sectioning, staining and microscopical examination. This was done, making sure of course that the photographing and fixing did not interfere in any way with the progress of development in the eggs.

Figure 1 shows the photographic record thus obtained. In connection with this figure, it should be mentioned that about one minute was required to carry out the manipulations of making each photographic exposure. Thus, the photographs for normal eggs and normal sperm were taken one minute before the time indicated in the figure, and those for normal eggs and irradiated sperm, one minute after. This does not detract from the significance of the figure but should be taken into account.

Examining Figure 1, two points of interest are apparent pertaining to the question which has been raised.* The first is that the marked delay in the onset of cleavage, caused by the irradiation of either gamete, is clearly manifest; and the second, that despite this, the appearance of the crescent stage is reached quite as quickly in case of the irradiated material as in case of the non-irradiated (Fig. 1, fifteen to twenty-five minutes). Thus, since in normal development, the crescent stage is reached after the fusion of the pronuclei, we may conclude that the entrance of the sperm, its movement through the egg cytoplasm, and its fusion with the egg pronucleus, are not impaired by the irradiation. Judging from Figure 1, it would seem, in fact, that this part of the cleavage cycle is speeded up, if changed at all by the irradiation. The slight enhancement indicated, however, is probably not significant because of the three-minute time interval involved in photographing the three sets of material.

The preserved material was fixed in Bouin's fluid, sectioned at a thickness of 5 mu and stained with Heidenhain's iron hematoxylin according to the well known procedure. Mass preparations were made so that the slides contained serial sections of actually hundreds of specimens. During the study of these, counts were made of the relative numbers of individuals in each sample that were in the stages listed above. The killing schedule together with the results of the counts are shown in Table 1.

Study of Table 1 yields quite the same impression one obtains by studying the slides directly. It is interesting, first of all, to note that control material fixed three minutes after insemination shows no sperm to be present within the eggs. Investigation of this disclosed that the fertilization membrane was swept away during the course of dehydration and that since the sperm had not passed through the membrane in this length of time, it likewise was swept away. Since, however, sperm were found within the cytoplasm when the material was fixed four minutes after insemination, it is clear that three to four minutes are required for the sperm to pass through the membrane. Considering the controls farther, the figures indicate that the stages mentioned above were recognized and that these bear the relationship to each other which is indicated in Figure 2 (upper part).

Comparing the figures for irradiated and non-irradiated materials, it becomes clear that Stage 3 (fusion of pronuclei) is reached at very nearly the same time irrespective of whether treatment is applied to the gametes, thus verifying the conclusion above obtained by observing living material. Examining the figures farther, it will be seen that treatment of the female gametes produces somewhat greater effects than treatment of those of the male. Not only is there greater delay, but also the mitotic phases are less distinct and are more difficult to identify. Parenthetically, it should be pointed out that this finding is not contradictory to the one described previously[2] to the effect that treatment of sperm appears to produce greater slowing than treatment of eggs. The difference is

* Other points of interest in this chart will be dealt with in subsequent papers.

TABLE I

Stage Number		0*	1	2	3	4	5	6	7	8	8+	Total Individuals Observed
	Minutes after fertilization when fixed											
Controls	3	100										100
	4		100	7								107
	7		33	56	17							106
	9				20	100						120
	10				50	95						145
	17					90						90
	27					90	1					91
	33					15	90	7				112
	38						2	100	3			105
	43							17	90			107
	46								29	99		128
Irradiated eggs plus normal sperm	5		100	10								110
	8		55	60	30							145
	11				43	180						223
	28					90						90
	54					36	10	1				47
	87						90	1				91
	110						69	10				79
	133						68		30			98
	141						7		35			42
	150						11		40			51
Normal eggs plus irradiated sperm	6		90	3								93
	9		9	78	8							95
	12			1	50	190						241
	29				3	90						93
	55					40	70					110
	89						107	5				112
	109						82	100	15	15		212
	131								20	90	5	115
	142							1	19	85	25	130
	151								4	18	82	104

* Fertilized but without sperm in the egg cytoplasm.

due to the fact that a lower intensity of radiation (720 r/min.) was used previously and that so much recovery occurred in the eggs during treatment with this intensity that they actually displayed less irradiation effect when measured. An abundance of data has been obtained on this point although it has not been published as yet.

Next, an attempt was made to determine just how the time relationships of the various stages had been shifted with respect to each other. It has already been shown that Stages 1, 2 and 3 are passed through quite as quickly whether radiation is applied or not, thus leaving question only in regard to the mitotic phase of the cleavage cycle. For this, Table 1 as well as the fixed material was studied carefully with the idea of fixing the time limits of the different stages as precisely as possible. The results are shown in Figure 2.

The diagrams in the upper part of the

figure serve as an index for the graphs below. The graphs (two, upper and lower) are made up of rectangles, the width of which indicates the relative time limits of the different stages. In the upper, it will be seen that the controls—that is, normal sperm (N.S.) plus normal eggs (N.E.)—Stages 1, 2 and 3 are passed through very quickly. The limits of Stages 1, 2 and 3 and 6, 7 and 8 could be established sharply only in case of the controls, so that Stages 1, 2 and 3 were considered together and likewise Stages 6, 7 and 8. In case of the normal sperm (N.S.) and irradiated eggs (I.E.) it will be seen that the time between the beginning of Stage 4 and the end of Stage 8 is much greater than in case of the controls, and also that in case of irradiated sperm (I.S.) and normal eggs (N.E.) essentially the same thing is shown except that the amount of delay is not as great. Thus since Stages 1, 2 and 3 are the same in the three cases, the upper graph is in accord with what has been indicated above and in addition has the limits of certain of the mitotic phases indicated.

Now, in order to determine which stage of the mitotic part of the cycle is delayed the most, if any, the lower graph was prepared. Since Stages 1, 2 and 3 were unaffected by the irradiation, they are reproduced in the lower graph the same as in the upper. The linear dimension of the other parts, however, was increased in the case of the controls and irradiated sperm to have the same length as in the case of irradiated eggs, the change for each separate stage being increased in proportion to the total amount in each case. Examining the relationships, then, two things

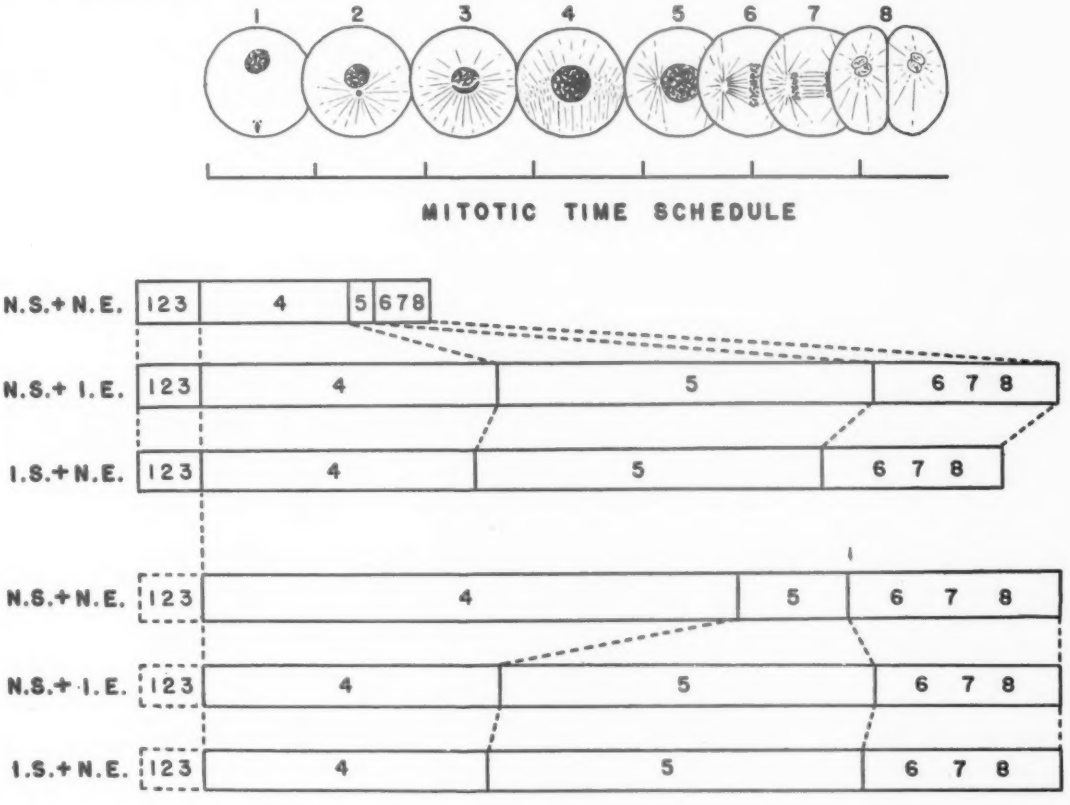

Fig. 2. At the top, diagrams showing the mitotic time schedule. Beneath, graphs showing the influence of roentgen rays on the time duration of the various stages in the cleavage cycle. See text for complete description.

become evident: (1) that all of the stages in the mitotic phase of the cleavage cycle are delayed by the treatment, and (2) that Stage 5, the prophase, seems definitely to be delayed more than the others.

It would seem, therefore, that as the cell enters the phase of forming chromosome bodies, it experiences the greatest injury derived from exposure of the gametes to radiation.

SUMMARY

1. It has been found that the exposure of sperm or eggs of *Arbacia punctulata* to large doses of radiation (62,400 r) does not retard the entrance of the sperm into the egg, its movement through the egg cytoplasm or its fusion with the egg nucleus.

2. Further, it was found that whereas all phases of the mitotic part of the first cleavage cycle are delayed, the prophase stage was slowed to the greatest extent.

REFERENCES

1. FRY, H. J. Studies of the mitotic figure. V. The time schedule of mitotic changes in developing *Arbacia* eggs. *Biol. Bull.*, 1936, *73*, 89–99.
2. HENSHAW, P. S., and FRANCIS, D. S. The effect of x-rays on cleavage in *Arbacia* eggs; evidence of nuclear control of division rate. *Biol. Bull.*, 1936, *73*, 28–35.

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FURTHER STUDIES ON THE ACTION OF ROENTGEN RAYS ON THE GAMETES OF *ARBACIA PUNCTULATA*

III. FIXATION OF IRRADIATION EFFECT BY FERTILIZATION IN THE EGGS

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WE HAVE shown previously* that exposure of *Arbacia punctulata* eggs to roentgen rays causes a delay in the occurrence of the first cleavage, and further, that if an interval of time is allowed between the end of treatment and the moment of insemination, the effect is lost or reduced as a function of time—the latter being a change which has been called *recovery*.

While these findings were satisfactory in demonstrating that recovery takes place so far as the first cleavage is concerned, they gave no information as to whether recovery is significant for subsequent cleavages and later development or whether it continues after fertilization. It is the purpose of this report to deal with these points.

The procedure employed was as follows. Eggs and sperm were collected in the usual way from a single female and male. The collection of eggs was divided into two lots, one of which served as experimental and the other as control material. One lot was divided, placed in two small dishes and exposed to roentgen rays, one at 20 cm. and the other at 28.3 cm. distance from the target of the roentgen tube.

The roentgen-ray equipment used was the low voltage apparatus available at the Marine Biological Laboratory. The only reason for using this equipment was that no other was available at the time we wished to work. The outfit was operated at 120 kv. and 5 ma. and the intensities at the points of treatment were 720 and 360 r/min., respectively, as measured in air with a small celluloid ionization chamber, no filter being used. The duration of exposure was forty minutes, making the doses respectively 28,800 and 14,400 r.

Following treatment, each lot of treated material was divided into eight parts and placed in Syracuse watch dishes containing 10 cc. of sea water each. Samples of each lot were then inseminated with normal sperm at the following times after the end of treatment: 0, 10, 20, 40, 60, 80, 120 and 180 minutes. Control samples handled in precisely the same way, except for treatment, were also inseminated with normal sperm, one sample immediately at the end of the treatment period and another 180 minutes later. All samples were then allowed to develop for forty-eight hours, care being taken to keep temperature and other factors the same in each sample.

At the end of the forty-eight hour period, the organisms in all of the samples were killed (with 2 per cent formaldehyde and sea water) and classified as to degree of development. For this, technique essentially the same as that employed by Mavor† was used. At forty-eight hours practically all of the control organisms had developed into well formed plutei larva with arms appreciably longer than the rest of the body. This stage represented the most advanced development and was called No. 1. The irradiated material showed various degrees of development which may be listed as follows: No. 2—the two main arms equal to the rest of the body; No. 3—arms shorter than the body; No. 4—stump arms or triangular shaped gastrula; No. 5—gastrula; No. 6—blastula;

* See the papers just preceding.

† Mavor, J. W., and De Forest D. M., The relative susceptibility to x-rays of the eggs and sperm of Arbacia. *Proc. Exper. Biol. & Med.*, 1924–1925, *22*, 19–21.

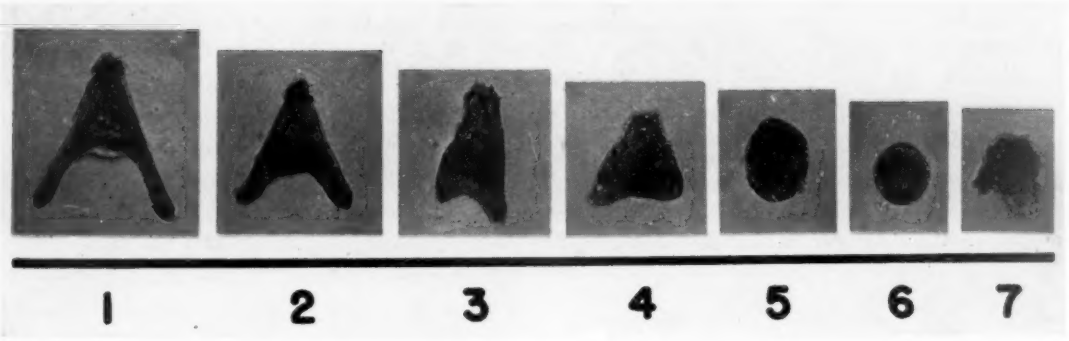

FIG. 1. Photographs showing the various degrees of development observed (see text for description).

and No. 7—no development (usually considerable disintegration). The various stages as observed are shown in Figure 1.

Classification was carried out on a quantitative basis by observing the samples under a microscope and counting the number of organisms in a given field that were in each stage. If necessary, several such fields were counted in order to make the total number of organisms observed over one hundred in each case. The values obtained were then placed on a percentage basis so that the results of different experiments could be compared.

Tabulation of the results in this manner gave the relative numbers of organisms in each sample that had reached the different stages, but we were in need of some numerical value that would represent the degree of development, or average development, of each sample in order that the advance of the different samples could be compared. Following Mavor's technique still farther, such a value was obtained by multiplying the relative number of organisms in each stage by the stage number and adding together the values thus obtained. It will be seen that by this procedure, the

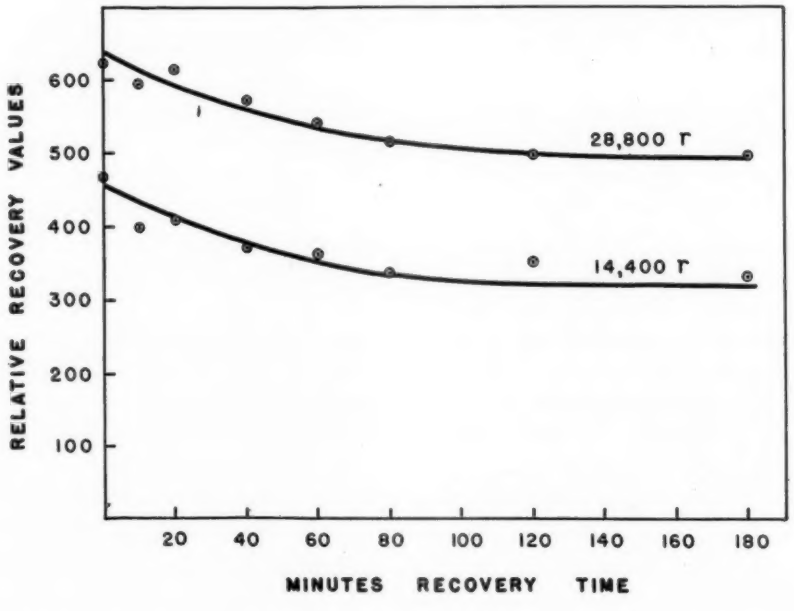

FIG. 2. Curves showing the degree of development after exposure to roentgen rays and various times allowed for recovery between the end of treatment and the moment of insemination.

greatest amount of development among the different samples will be represented by the smallest numbers, and conversely, that the largest amount of injury will be represented by the largest numbers. The intervals between the stages, of course, are not the same, causing the values to vary among themselves; nevertheless, the averaged values follow a general trend consistently enough to allow deductions that lead to the answer sought.

just the averaged figures in order to obtain a correct impression of what occurred and to evaluate the results properly. Consider the results for the control material. The reason for inseminating non-irradiated organisms both at 0 and 180 minutes after the end of the treatment period was to make certain that aging alone did not injure the eggs. If one considered only the averaged values, it would appear that aging improves the developmental possibilities.

Table I

	Non-Irradiated		Irradiated							
Minutes after treatment when fertilized	0	180	0	10	20	40	60	80	120	180
Exp. No.			28,800 r							
1	193	198	561	521	556	493	499	509	445	428
2	198	194	614	603	673	620	517	514	566	540
3	196	192	644	602	638	651	569	458	503	464
4	150	138	616	692	688	693	693	668	680	689
5	258	143	688	673	669	574	594	568	445	516
6	465	244	695	651	643	565	608	608	514	573
7	158	153	545	445	437	408	333	310	352	328
Av.	231	180	623	598	614	572	544	519	500	505
			14,400 r							
1	193	198	332	348	317	325	302	282	295	276
2	198	194	489	422	387	325	381	336	301	298
3	196	192	510	310	407	255	329	244	259	254
4	150	138	525	504	665	588	668	654	563	606
5	258	143	527	424	465	324	390	356	326	241
6	465	244	618	549	384	565	295	333	474	481
7	158	153	286	246	249	219	201	164	242	174
Av.	231	180	469	400	410	371	366	338	351	332

The results for seven experiments, carried out on different collections of material and on different days, are given in Table 1. The averaged values, shown in the last column, are plotted in Figure 2 where the abscissae show the time after treatment ended when the eggs were fertilized and the ordinates the averaged values in each case representing the degree of development.

On going over the data in Table 1, it is seen that one must consider more than

But, if one considers the individual experiments, it will be seen that the discrepancy comes largely from one experiment (Exp. 6) where some accidental injury was apparently inflicted on the control sample which was inseminated immediately at the end of the treatment period. From the other six experiments, it is clear that three hours' aging does not alter the response of the controls in any significant way and that the values for the control samples may be com-

pared directly without correction or adjustment.

Considering the data for the irradiated material, it will be seen that the values are somewhat irregular. This may be due largely to two things: (1) that the test material was not in the optimum condition since the experiments were carried out late in the spawning season for *Arbacia;* and (2) because the developmental stages used did not involve the same time intervals, as mentioned above. Since, however, the variation appears to be of a heterogeneous character, the results for a number of experiments are more dependable and the averaged results indicated by the curves may be taken as the most reliable evidence of the degree of development attained after the various times allowed for recovery.

For either dosage used, it is clear that the beginning of the curves is at a higher level than at the end, that the downward trend starts at the beginning, and that the descent is more rapid near the beginning than near the end.* It is clear, therefore, that development had proceeded farther in those samples which had been allowed the most time for recovery, and that the curves bear characteristic similarities to those based on delay in the occurrence of the first cleavage, furnishing us with the answer we set out to obtain. Since the recovery time following fertilization was long compared to that before, it follows that little, if any, recovery took place after fertilization and accordingly that fertilization acts to stop the recovery process, thus preserving whatever irradiation effect was present at the moment of fertilization.

* The slope of the curves and the point at which they level off are not significant here for these characters are determined by the method of measurement.

SUMMARY

On the basis of the above observations, it appears that the recovery from irradiation effect which takes place before fertilization and is manifest at the time of occurrence of the first cleavage is significant in subsequent cleavage and later development; and consequently, that fertilization acts to fix whatever irradiation effect is present at the moment of fertilization.

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FURTHER STUDIES ON THE ACTION OF ROENTGEN RAYS ON THE GAMETES OF *ARBACIA PUNCTULATA*

IV. CHANGES IN RADIOSENSITIVITY DURING THE FIRST CLEAVAGE CYCLE

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IN THE previous reports, it has been shown that application of hard roentgen rays to the germ cells of *Arbacia punctulata* before fertilization causes a delay in the occurrence of the cleavage process following fertilization. It is the purpose of this report to deal with the delay effect obtained not only by exposure before fertilization, but also at various times thereafter; in other words, to compare the radiosensitivity of the gametes with the zygote and to determine the changes in radiosensitivity which occur during the first cleavage cycle.

The roentgen-ray equipment used was the dual-tube self-rectification outfit available at the Marine Biological Laboratory and the simultaneous cross-firing technique was employed. The equipment was operated at 194 kv. and 25 ma., and the beam of roentgen rays was unfiltered except for the heavy glass of the roentgen tube and the bakelite windows of the tube shield (equivalent to a filter of 0.2 mm. of copper). The output intensity, as measured in air with a small celluloid ionization chamber, was 7,800 r/min. at the point of treatment —9.5 cm. from the center of each target. The exposure periods were varied for different experiments as indicated below.

Sperm and eggs were collected in the usual way from single individuals and handled with the precautions necessary for this kind of work. For each experiment carried out, material was treated as follows: "dry sperm," a concentrated egg suspension and a diluted egg suspension were placed under the roentgen machine in separate small celluloid containers. In addition, a reserve supply of diluted egg suspension was kept in a large glass container. Then, just before throwing the switch which started the exposure, the diluted egg sample under the roentgen machine and the reserve supply were inseminated. For the first experiment to be described, the exposure was for four minutes (31,200 r). At the end of treatment irradiated sperm were allowed to fertilize samples of both normal and irradiated eggs, and likewise, normal sperm were allowed to fertilize normal and irradiated eggs. The following combinations were thus produced:

(1) Normal Eggs (N.E.) + Normal Sperm (N.S.) (Controls)
(2) Normal Eggs + Irradiated Sperm
(3) Irradiated Eggs + Normal Sperm
(4) Irradiated Eggs + Irradiated Sperm
(5) Irradiated Zygotes

Besides these, separate samples of zygotes from the reserve supply were given the same identical treatment at 5, 10, 15, 20, 25, 30, 35, 40 and 45 minutes after insemination. All samples were then watched and the time when 50 per cent cleavage had occurred in each case was carefully determined.

A number of such experiments was carried out and the same kind of results was obtained in each case. Since a table of data would add little to what is to be said, such is being omitted and the averaged values presented in graphs. Figure 1 shows the results obtained for the experiment as

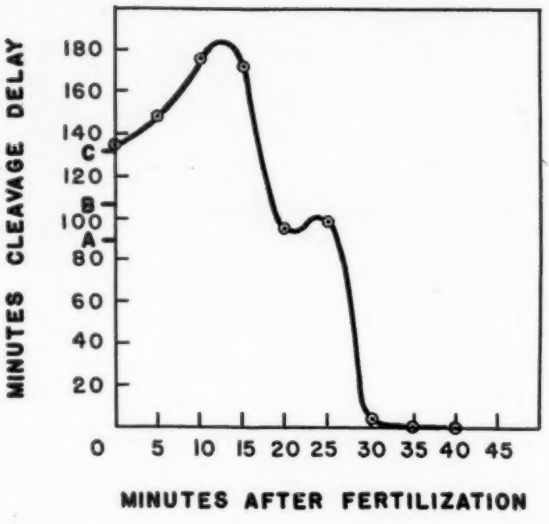

FIG. 1. Graph showing the relative radiosensitivity of irradiated eggs fertilized with normal sperm (*A*), normal eggs fertilized with irradiated sperm (*B*), irradiated eggs fertilized with irradiated sperm (*C*), and the zygote at various times after fertilization.

described above. The abscissae in the figure represent minutes after fertilization when treatment began and the ordinates the minutes' cleavage delay (i.e., over and above the cleavage time of the controls). The levels *A*, *B* and *C* on the ordinate axis indicate the cleavage delay obtained when sperm alone, eggs alone and both are treated, respectively.

It will be seen, therefore, that for the same dose of radiation, a greater effect is obtained when eggs are treated than when sperm are treated and that the effect is still greater when both gametes are treated. These findings are thus in accord with those of the second paper of this series.

It will be seen, moreover, that the newly formed zygote and the zygote whose gametes received similar treatment just prior to fertilization have essentially the same radiosensitivity. Following this, however, the susceptibility increases for a period of ten to twelve minutes (for the conditions used) after which there is a sharp decline interrupted only by a single slight shift of some kind. The slight ripple in the descending portion of the curve was suspected at first of being due to some experimental irregularity and that it would not be manifest in subsequent experiments. This was not the case, however, for it was displayed to some extent in every experiment carried out and when other doses of radiation were used as will be seen below. Thus, although we shall be unable to attach any significance to this finding, it must represent a real response of some kind.

Figure 2 shows the curve just described together with similar ones for samples of material that had received one and two minutes' exposure to the same radiation. From this it is apparent that although a correspondingly lesser effect is manifest in the two cases, the curves nevertheless show the same general characteristics. A peak in susceptibility is reached between ten and fifteen minutes after fertilization and a slight ripple is displayed in the descending portion of the curves.

In an attempt to analyze these results, Figure 3 was prepared. Fry's mitotic time schedule, as adapted for use in the second paper, is shown diagrammatically at the

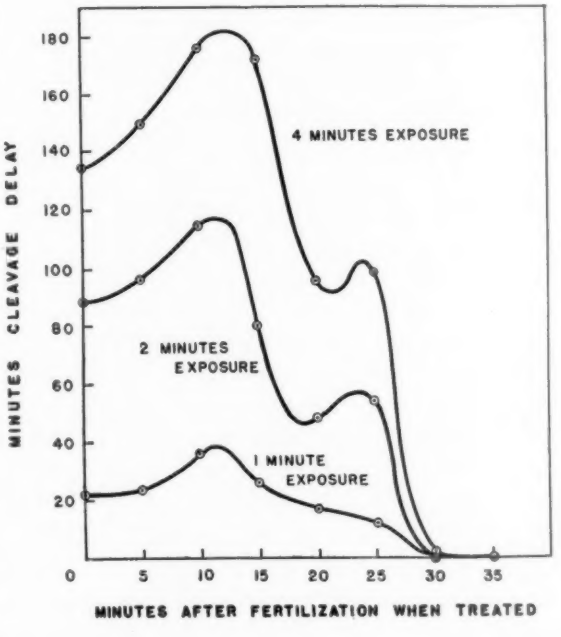

FIG. 2. Curves the same as that shown in Figure 1, but for various amounts of exposure.

top. Immediately beneath and laid out to the same time scale (i.e., the abscissae) is a reproduction of the curve from Figure 1. Below are curves showing changes in viscosity, permeability and oxygen uptake as described by Heilbrunn,[1] Fry and Parks,[2] Lillie[3] and Whitaker.[4]

From Figure 3, it will be noted that the first and main peak of susceptibility to radiation is reached shortly after the pronuclei have come together and that the second peak is reached during the early prophase stage. Moreover, it will be seen that the main peak in susceptibility is reached at very nearly the same time as peaks in viscosity and permeability and that there appears to be no significant relationship between radiosensitivity and rate of oxygen uptake.

From the results (Fig. 3) one might be inclined to attribute significance to the fact that the three upper curves show a peak at about the same time. However, before doing so, the following must be

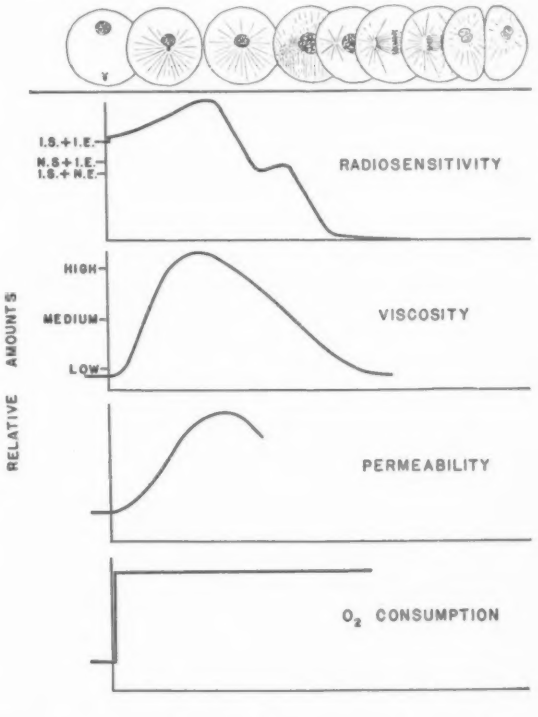

Fig. 3. Curves showing changes in radiosensitivity, viscosity, permeability and oxygen consumption at various times during the first cleavage cycle.

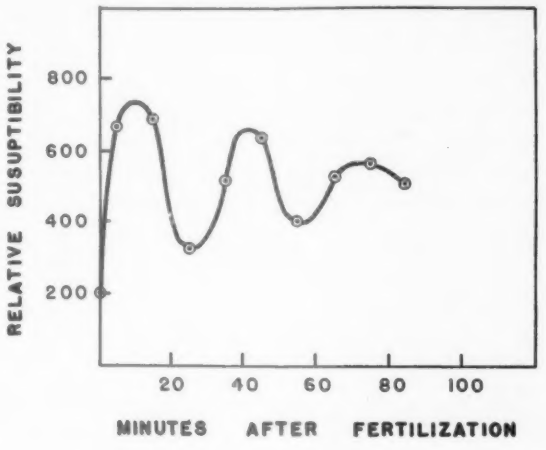

Fig. 4. Curve showing the changes in radiosensitivity which occur in the developing egg and made evident by measurements forty-eight hours after fertilization.

taken into account. It is clear from what has been said that the increase in radiosensitivity takes place only during the period before the fusion of the pronuclei. Thus, in view of the fact that recovery occurs in the egg before fertilization and is apparently stopped by fertilization (as shown in the third paper), it is possible that recovery continues in the egg pronucleus until it fuses with the sperm pronucleus. Should this be the case, it is obvious that as the time for recovery between the end of treatment and the fusion of the pronuclei becomes shorter, the effect for a given dose of radiation would be found to be greater, just as was the case. Furthermore, the more rapid ascent of the curves (Fig. 2) for the larger dosages is in accord with what would be expected if the increase in susceptibility were due to recovery. While there is not as yet any positive proof that the increase in susceptibility can be accounted for on the basis of recovery, this possibility cannot be excluded at this time.

Mistakes might also be made in attributing too great significance to the descent of the radiosensitivity curves, for as the actual cleavage is approached, there is less and less opportunity for the effect to become manifest should its manifestation in any way be latent. There are, however, two

points which make us believe that the descent is not due to lack of time for expression. The first is the constant appearance of the small ripple in the descending portion of the curves. Since it does appear so consistently, it would seem that the course of the curves here must be determined by something other than the method of measurement. The second point has to do with results obtained in another experiment.

In an attempt to obtain further information on the changes in radiosensitivity which occur during development, treatments were given at ten minute intervals during the first several cleavages and the degree of development noted after forty-eight hours, using the technique described in the report just preceding. Somewhat lower doses of radiation (3,600 r) were given in this case, however, since the organisms fail to survive to the later stages when the larger doses are administered. Moreover, softer radiation was used (140 kv., no filter), but this was only because no other was available at the time the experiments were carried out.

The results obtained are shown in Figure 4. It will be seen, as before, that although the effect is measured at a much later time in development, an increase in radiosensitivity is manifest during the first ten to fifteen minutes and that this is followed by a marked decrease. It would seem, therefore, that the decline of the curves (Figs. 1 and 2) cannot be attributed to the method of measurement and that it has to do with changes going on within the organism.

Parenthetically, Figure 4, in addition, shows certain other points not heretofore noted. Following the fall in radiosensitivity during the prophase, there is again an increase which reaches a peak at or just before the actual cleavage of the zygote. There appear, in fact, to be waves of susceptibility with peaks being reached at or near the times of the first and second cleavage. These, however, have little bearing on the point in question.

SUMMARY

1. Experiments have been carried out to compare the radiosensitivity of gametes and zygotes of *Arbacia punctulata* and to determine the changes in radiosensitivity which occur during the first cleavage cycle.

2. It was found (1) that the eggs are more susceptible than sperm when an intensity of 7,800 r/min. is used; (2) that for equal doses of radiation, the effect obtained by irradiating the zygote is greater than that obtained by treating either gamete alone; (3) that about the same effect is obtained when both of the gametes are given the same treatment as the zygote; and (4) that by two different methods of measuring the irradiation effect, the zygotes were found to increase in susceptibility until about the time the pronuclei fused and that they decreased in susceptibility during the prophase stage.

3. It was shown that the peak in susceptibility is reached at or about the same time as the peaks of viscosity and permeability are reached and that there is apparently no correlation between changes in radiosensitivity and rate of oxygen uptake.

4. It was pointed out that since the radiation effect is apparently produced in the nuclei and since recovery occurs in the egg only and then only until fertilization, the increase in susceptibility before fusion of the pronuclei may be due to recovery continuing in the egg pronucleus until the time of fusion.

REFERENCES

1. HEILBRUNN, L. V. The viscosity of protoplasm. *Quart. Rev. Biol.*, 1927, *2*, 230–248.
2. FRY, H. J., and PARKS, M. E. Studies on the mitotic figure. IV. Mitotic changes and viscosity changes in the eggs of Arbacia, Cumingia and Nereis. *Protoplasma*, 1934, *21*, 473–499.
3. LILLIE, R. S. Increase of permeability to water in fertilized sea-urchin eggs and the influence of cyanide and anesthetics upon this change. *Am. J. Physiol.*, 1918, *45*, 406–430.
4. WHITAKER, D. M. On the rate of oxygen consumption by fertilized and unfertilized eggs. V. Comparisons and interpretation. *J. Gen. Physiol.*, 1932–1933, *16*, 497–528.

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FURTHER STUDIES ON THE ACTION OF ROENTGEN RAYS ON THE GAMETES OF *ARBACIA PUNCTULATA*

V. THE INFLUENCE OF LOW TEMPERATURE ON RECOVERY FROM ROENTGEN-RAY EFFECTS IN THE EGGS

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IT HAS been shown previously that exposure of the eggs of *Arbacia punctulata* to roentgen rays causes a delay in the occurrence of the first cleavage, and further, that if time is allowed between the end of treatment and the moment of insemination, the effect will become reduced or lost —a process which has been called *recovery*.* In an attempt to shed more light on the nature of this reaction, an experiment has been carried out to determine whether the recovery process is affected by lowering temperature.

The procedure used was as follows: Eggs were treated in the manner described previously, enough radiation being given to produce an appreciable amount of cleavage delay. At the end of treatment, the eggs were divided into two lots, one of which was maintained at room temperature (24°C.) and the other which was placed in a tubular glass container and submerged in a beaker of water and chipped ice (0°C.). Non-irradiated controls were also kept under the same conditions at 24 and 0°C. At 0,† 60, 120 and 180 minutes after the end of treatment, samples of the irradiated and non-irradiated materials kept at the different temperatures were fertilized at room temperature and the cleavage time carefully determined also at room temperature.

A series of seven different experiments was performed, all of which showed the same general effect. Since the procedure was not exactly parallel in all of these, data for a typical experiment only will be presented. Such is shown in Figure 1.

It will be noted first of all that keeping a sample of non-irradiated controls at 0°C. for a period of three hours did not alter the cleavage time and likewise that aging in this particular case did not alter the cleavage time. It is safe, therefore, to compare the experimental samples directly.

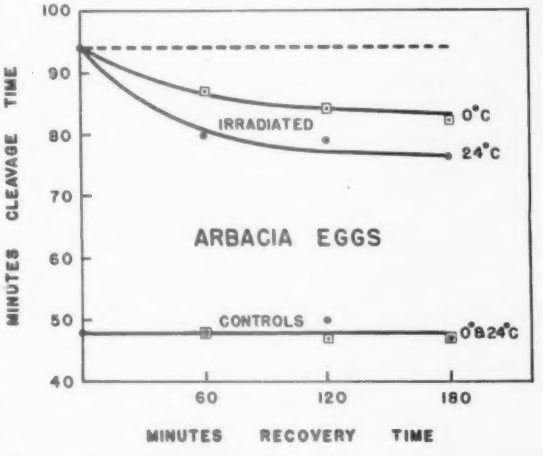

FIG. 1. Curves showing the effects of temperature on recovery from roentgen-ray effects in *Arbacia* eggs.

The curve for material kept at 24°C. is typical of a great many we have obtained by this procedure. It drops away rapidly at first but tends to become parallel with the base line. It is obvious that if the lower temperature prevented any recovery from taking place, the experimental points so obtained would have fallen along the dotted line at the top of the figure. Similarly, it is evident that if it did not influence the recovery process in any way, the points would have fallen along the curve obtained for room temperature. As made evident by the figure, they did not fall in either of these places but intermediate. It is clear,

* See the third paper of this series.
† That is, immediately at the end of treatment.

therefore, that temperature does have an effect on the recovery process, lower temperature tending to reduce it.

While this finding is of interest, knowing just how the rate of recovery varies with temperature would permit considerably more analysis. In conclusion, therefore, we are able to say only that lowering temperature from 24 to 0°C. reduces the amount of recovery observed.

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FURTHER STUDIES ON THE ACTION OF ROENTGEN RAYS ON THE GAMETES OF *ARBACIA PUNCTULATA*

VI. PRODUCTION OF MULTIPOLAR CLEAVAGE IN THE EGGS BY EXPOSURE OF THE GAMETES TO ROENTGEN RAYS

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IN THE preceding reports attention has been called to the production of one particular effect in *Arbacia punctulata* eggs caused by exposure of the gametes to roentgen rays—namely, delay in development and especially delay in the occurrence of the first cleavage. In the present instance, attention is to be called to abnormalities of development, particularly multipolar cleavage.

It was observed in connection with the work described in Papers I, II and IV of this group, that, in addition to delay in the first cleavage being caused by irradiation, cleavage is often abnormal in that more than two blastomeres were formed. This is made especially evident in the chart, Figure 1, Paper II. Referring to this chart, it will be seen that when cleavage finally occurs in those specimens receiving radiation, a large proportion of the divisions are multipolar in character, and further, that this is the case irrespective of whether the radiation is applied to the sperm or the eggs.

That multipolar cell division may be produced by exposure of cells to high energy radiation has been mentioned by several investigators (Hertwig, O.;[4] Hertwig, G.;[5] Packard;[9,10] Strangeways and Hopwood;[12] Politzer, 1934; Sonnenblick[13]) and while some importance has been attached to the observation, the information available has not been sufficient to allow really significant deductions. In the present case, the effect has been obtained with such ease that a variety of experiments has been carried out and considerable information obtained. Among other things, we shall discuss what appears to be an important mechanism of cell death and how irradiation may, by the same mechanism of action, produce either death or malignancy.

SPECIAL CONSIDERATION

At the outset it is interesting that both delay and multipolarity should be caused by the same treatment, for it is clear that the two mechanisms of response are governed by quite different principles. Cleavage delay is a *cumulative* process in each cell, a fact which is made especially clear in Figure 1 of the first paper. Except for extremely low doses, some effect is manifest in every cell and the amount of effect displayed by each cell increases as the amount of radiation applied is increased. Multipolar cleavage, on the other hand, is an *all-or-none* process—either the abnormality occurs or it does not. Aside from the number of cells formed at the time of cleavage (cf. below), it is evident that various degrees of this effect cannot be observed in the organisms and that increasing the dose of radiation could manifest a greater effect only by producing the abnormality in a greater proportion of the organisms in a sample receiving treatment. Parenthetically, it seems that two better examples could not be obtained to illustrate the characteristic differences between the cumulative and the all-or-none types of response.

Although the two effects are manifest at the same time in the same organisms and caused by the same radiation treatment, question arises as to whether there is really a close relationship between the two responses. To investigate this and the significance of multipolar cleavage, extensive use has been made of the fixed material described in Paper II and certain experi-

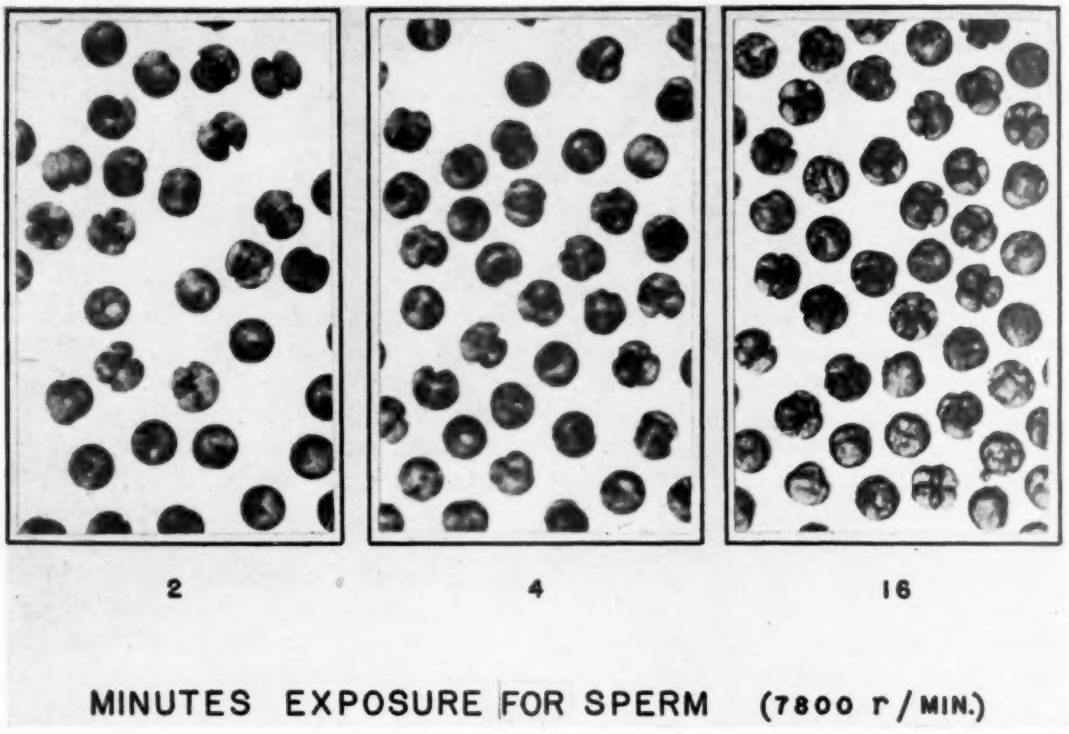

FIG. 1. Photomicrographs arranged to show that the proportion of organisms manifesting multipolar cleavage varies with dose of radiation administered.

ments have been carried out. The various points will be taken up in much the same order as investigated.

POLYSPERMY

In view of the fact that polyspermy is known to produce multipolar cleavage (Boveri,[1] and others) and that radiation applied to gametes has been said to induce polyspermy (Packard[10]), it was suspected that this condition might be responsible for the multipolar cleavage observed in the sea urchin material. To investigate this point, serial sections of eggs fixed when the two pronuclei are clearly visible were examined for the presence of extra sperm pronuclei. In fact, complete series of serial sections of more than one hundred treated individuals and more than one hundred nontreated control individuals were examined.

Positive identification of sperm pronuclei is a tedious task, yet one that can be done with reasonable certainty if good preparations are available and proper precautions taken. In the material in question, the sperm pronucleus is accompanied by a sperm aster which is rendered conspicuous by Heidenhain's iron hematoxylin stain. This was always used as the final distinguishing feature in identifying the sperm pronucleus.

Of the 100 control specimens examined, all except two were found to contain a single sperm pronucleus and these had two. Examination of a similar number of treated specimens revealed about the same situation. In this case also, all except two were found to contain a single sperm pronucleus and of these, one had two and it was doubtful whether the other had one or two. Thus, since other samples of the same treated material displayed a high percentage of multipolar cleavage, it was clear that the multipolar condition as observed here was not due to polyspermy.

PHASE RELATIONSHIPS OF CYTOKINETIC AND KARYOKINETIC RHYTHMS

Since delay and multipolarity are both caused by the same treatment, the question arose as to whether the division rhythms of the nucleus and cytoplasm may not have been thrown out of phase—that is, whether cytoplasmic division alone may not have been slowed to such an extent that the second or third nuclear division occurred in phase with the first cytoplasmic division, thereby causing the multipolar condition.

The fixed preparations were studied for an answer to this question. Briefly, a large number of individuals fixed at different times during the mitotic phase were examined and in no case was a specimen found which showed nuclear division without at the same time showing evidence of cytoplasmic division. It thus became certain that the cytokinetic and karyokinetic rhythms were not disturbed in their relation to each other.

DOSE AND MULTIPOLAR CLEAVAGE

One of the first questions to arise in connection with the multipolar cleavage phenomenon was the relation between dose of radiation applied to one of the gametes and amount of multipolar cleavage produced.

The chart, Paper II, shows that a dose of 62,400 r applied either to sperm or eggs before fertilization produces a high percentage of multipolar cleavage. Thus, the problem was to determine how this percentage might vary if the dosage was varied. Figure 1 shows photomicrographs taken in connection with the work presented in Paper I. It will be noted that there are definitely more multipolar cleavages occurring in the second photograph (four minutes' exposure) than in the first (two minutes' exposure), but that the second and third are about the same. Thus it is clear at the outset that the amount of multipolar cleavage varies to some extent with dose of radiation applied. In connection with the work reported in Paper I rather rough determinations were made, in

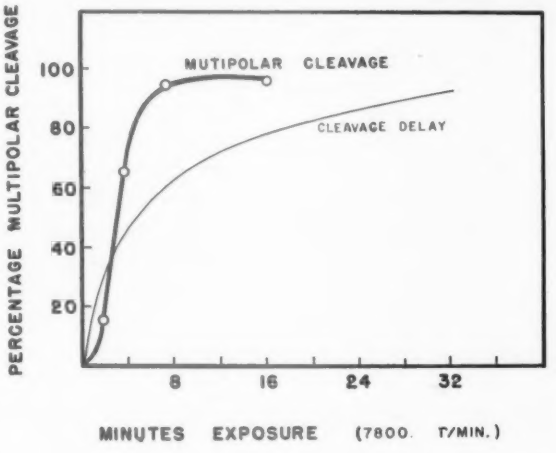

Fig. 2. Curves showing how multipolar cleavage and cleavage delay vary with the dose of radiation applied. The abscissae show the minutes' exposure to roentgen rays and apply to both curves. The ordinates show percentage multipolar cleavage and apply only to the heavy curve. The light curve is a reproduction of the one shown as Figure 2, Paper I.

the case of five experiments, of the percentage of multipolar cleavage occurring when various exposures were administered. The values obtained are shown in Table I. While the number of observations shown is small and the precision used in obtaining the values was of a low order, the data are, nevertheless, adequate to show a number of the characteristics of the response.

It will be seen that the reaction has a definite threshold and that it goes to completion within a fairly narrow range of dosage. Moreover, it will be seen that the radiosensitivity of different collections of material varies rather markedly (this being less than the lowest exposure given in the case of Exp. 7). It should be stated that an occasional multipolar cleavage appeared among the controls but that the total number never exceeded 1 per cent. Taking the values for Experiment 5 as an example, Curve *A*, Figure 2, is obtained. This is generally sigmoid in character, having a toe, a rapidly ascending portion and a flattening portion. The shape, therefore, indicates graphically that an appreciable amount of radiation must be administered

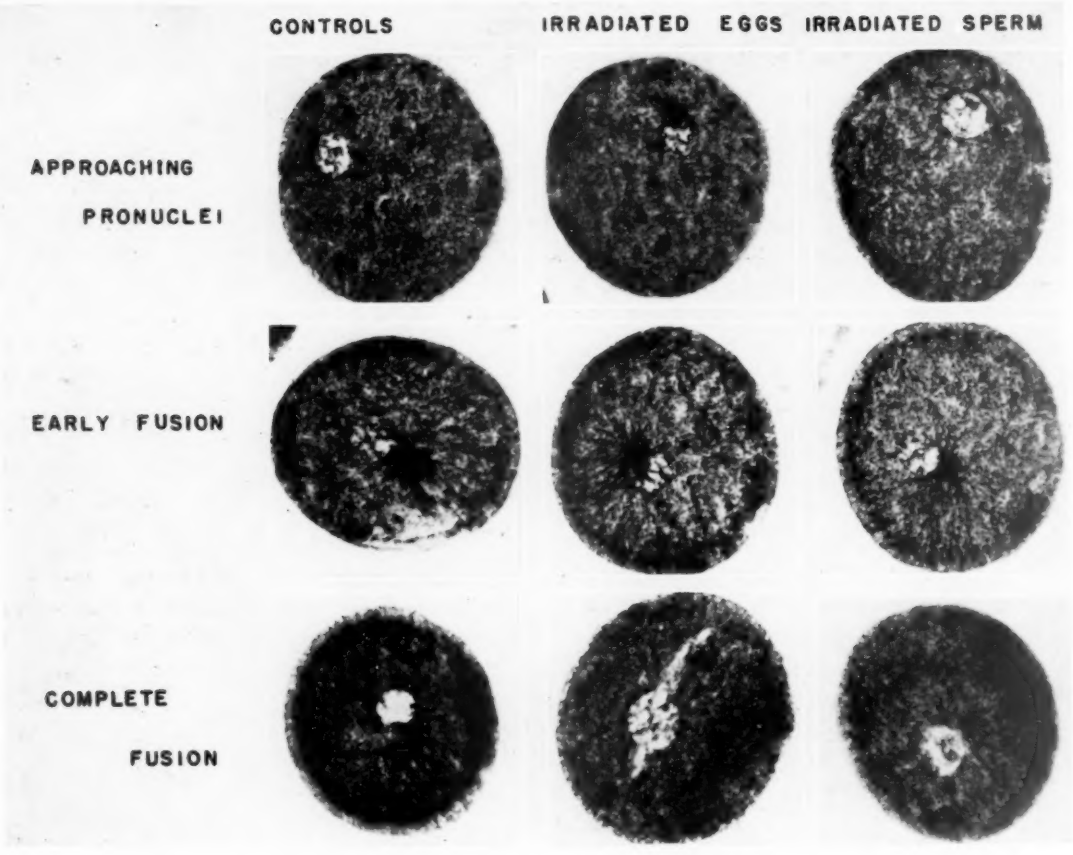

FIG. 3. Photomicrographs arranged to show that fusion of the pronuclei is complete irrespective of whether one or the other gamete has been exposed to a heavy dose of radiation (62,400 r). In the lower row, the middle figure shows the crescent stage. It is different from the other two only because it is a little older. Either the crescent stage or the precrescent stage could have been selected with equal ease in all three cases. This selection is shown merely for variety.

before any effect is observed among the organisms and that most of the cells respond to about the same dose.

Thus, whereas the dose-effect curve for cleavage delay characterizes the rate at which something is being changed in each organism, the dose-effect curve for multipolar cleavage characterizes the rate at which the population of individuals responds in a particular way as the radiation is varied. Thinking in terms of the discrete action of radiation, this means that each unit action (of a particular kind) contributes to the observed effect in each organism in the first case, and in the second that no visible effect is produced until a certain number of such unit actions have occurred, at which time the effect becomes manifest completely. It is to be emphasized, therefore, that if both curves (Fig. 2) were exponential* as is the one for cleavage delay, the interpretation to be adduced would be quite different in the two cases. In case of cleavage delay, as has been stated, the exponential character suggests that the reaction is dependent upon the rate at which some particular substance is changed by the radiation, whereas in the case of multipolar cleavage it would suggest that the reaction is dependent upon a single action (all-or-none) event in each organism.

In conclusion, therefore, it is clear that the percentage of multipolar cleavage pro-

* All-or-none responses yielding exponential killing curves have been observed in the case of bacteria (cf. Lea, Haines and Coulson, also Lorenz and Henshaw).

duced by radiation does vary with dosage and that the reaction is of the multiple action type.

GYNOGENESIS AND ANDROGENESIS

Packard (1914) has stated that in the case of *Nereis* material, irradiated sperm may (1) stimulate the egg without being drawn into it, (2) stimulate and be drawn in without fusing with the egg nucleus, and (3) stimulate, be drawn in and fuse with the egg nucleus, but interfere with development. Development in the first two cases, therefore, is by gynogenesis. Packard states further that androgenesis may likewise be produced in this form by properly exposing the eggs. Other investigators (Hertwig, O.,[4] using frog material; Hertwig, G.,[5] using frog and sea urchin; Oppermann,[8] using trout; Dalcq,[3] using frog; and Simon,[11] using frog) have likewise stated that certain large doses of radiation applied to either gamete will allow fertilization but nevertheless prevent the irradiated pronucleus from participating in subsequent mitotic activity. In Paper II we have stated plainly that in the sea urchin material, as used by us, fusion of the pronuclei takes place quite as rapidly when one or the other gamete is heavily irradiated as when neither is irradiated. The evidence supporting this conclusion is based upon observations of living specimens and cytological examination of fixed material. In connection with the present consideration, we wish to indicate just how definite the cytological evidence is on this point and consider the possible meaning.

We have referred to the material studied as having been heavily irradiated (62,400 r applied to one of the gametes). Such reference would seem permissible in view of the fact that 500 to 600 r will produce a threshold skin erythema and since 5,000 to 10,000 r is the tolerance limit for a human patient even when the divided dose treatment is used and spread over a long period of time. Thus, while our cytological observations do not pertain to material receiving a variety of doses, some evidence of nonfusability of the pronuclei should have been manifest if this were an important factor in the present case.

Figure 3 shows photomicrographs of typical eggs at various stages during the early part of the first cleavage cycle. It will be seen that despite the application of a large dose of radiation to either gamete before fertilization, fusion of the pronuclei is as complete as though no radiation had been administered. Before discussing this point, however, the material of the next section will be presented since it bears on the same problem.

FIRST EVIDENCE OF MULTIPOLARITY

Since the multipolar cleavage observed could not be accounted for on the basis of polyspermy, differential slowing of the divisional rhythm of the nucleus and cytoplasm, or a tendency for the pronuclei to remain apart, it was decided to reverse the procedure and look for the first evidence of multipolar cleavage. Thus, we began with samples which showed outstanding displays of multipolar mitotic figures, and proceeded progressively back over those fixed at earlier periods in the mitotic cycle. The results of our findings are indicated in Figures 4 and 5. The lower rows show the types of mitotic figures which may be found, whereas the upper rows show the stage just previous. The stage preceding this is the one shown at the bottom of Figure 3, which, as indicated, is the same irrespective of whether radiation has been applied. It thus becomes evident that the multipolar condition, at least in some cases, begins with the appearance of supernumerary asters. Whether these arise *de novo* or from preëxisting asters is not yet apparent, but it seems abundantly clear that because of them, chromatin material predetermined under normal conditions for two blastomeres is distributed among more than two and sometimes several.

This raises the very interesting question of what initiates the formation of asters. In the present case, accessory ones are produced by irradiation of either gamete.

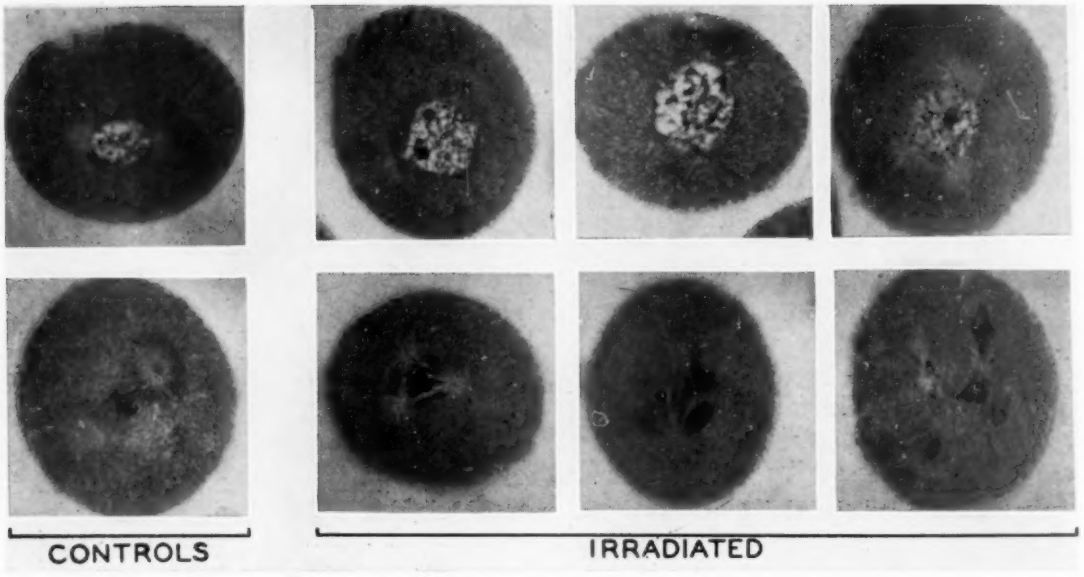

FIG. 4. Photomicrographs showing the mitotic configurations of zygotes whose sperm had received no radiation (controls) and whose sperm had received 62,400 r (irradiated).

In view of the fact that sperm contain almost no cytoplasmic material, it would seem that cytoplasmic changes are not responsible. Further, in view of the fact that the egg contributes no aster as does the sperm, it would seem that irradiation of this body is not responsible. The latter point is strengthened by the fact that the sperm aster apparently completely disappears following the crescent stage and is replaced by two new ones that are functional in mitosis. Consideration of these various points leads to the presumption that a change produced in the nuclear material (even a single gamete) by the irradiation, in some way induces the formation of accessory asters and that these in turn cause the chromatin to be divided several ways.

This is a reasonable deduction from the

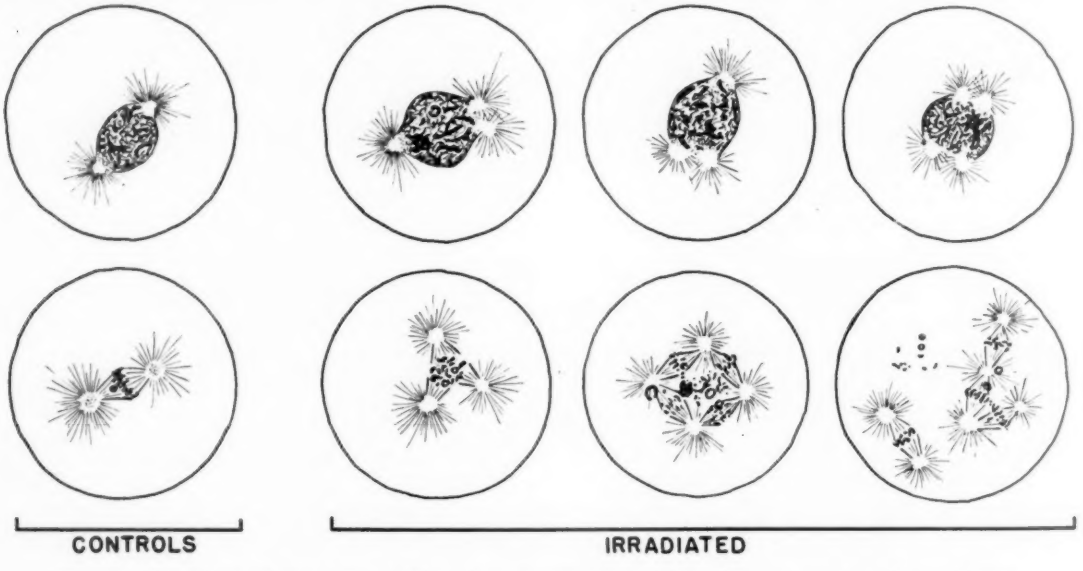

FIG. 5. Drawings of the figures (Fig. 4) as supplemented by adjacent sections in each case.

tri- and quadripolar mitotic figures (Figs. 4 and 5), for in these cases, it would seem that the homogeneous chromatin mass is simply drawn out to more than two poles, but this simple scheme would not seem to apply so readily in case of the lower right-hand figure where the mitotic configuration is a good bit more elaborate. It is difficult to understand how the chromatin in this case could have become so distributed if at the stage just previous it was localized in a single homogeneous mass. The elaborate figure might be expected to result more naturally from a condition in which the chromatin material is rather widely scattered at the stage just prior to the formation of spindles—as, for example, the incomplete fusion of pronuclei. With this in mind, our material was reëxamined to see whether any appreciable number of such figures appeared in the samples, and, if so, whether even traces of cytological evidence suggesting incomplete fusion of pronuclei could be found. Briefly, a fair proportion (20 per cent or more) of the mitotic figures were of the elaborate type and still no cytological evidence of incomplete fusion could be found—that is, aside from that which is to be given immediately below, but which in the end seems to confirm this conclusion.

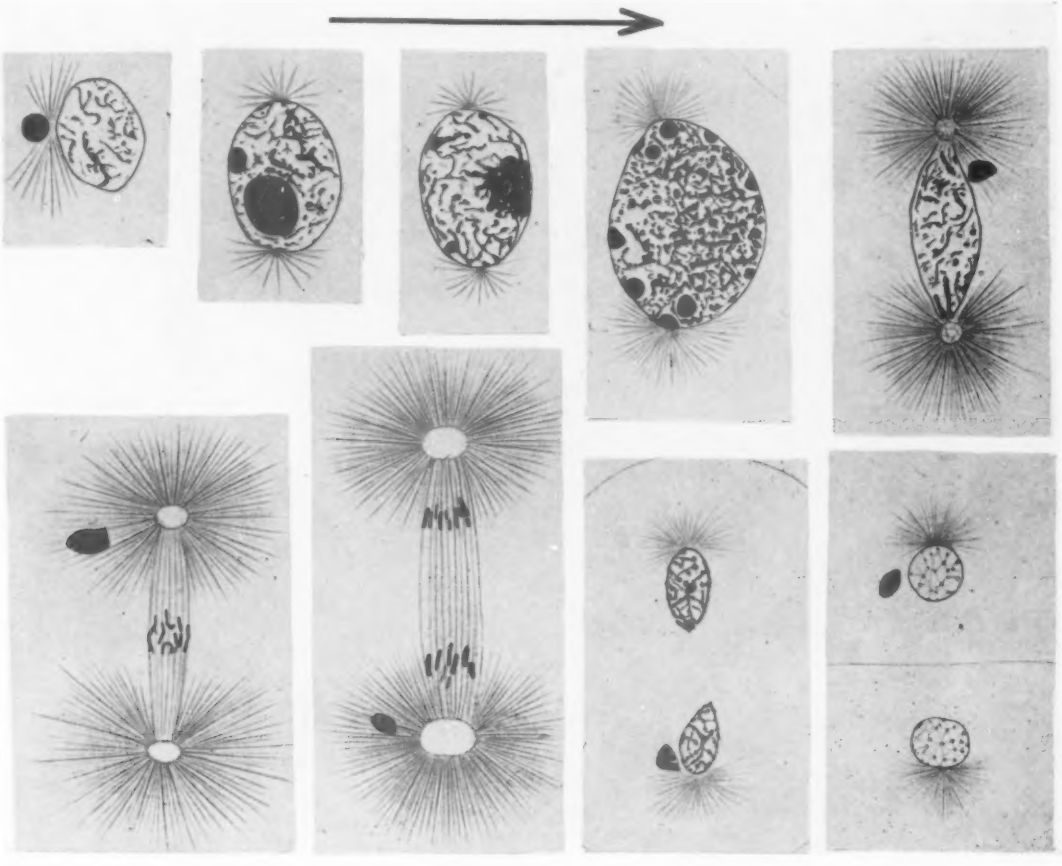

Fig. 6. Reproduction of Hertwig's figures showing evidence of sperm pronuclear material which did not enter into fusion with the egg pronucleus. Note that the identity of the sperm material becomes almost, if not completely, lost.

Strong evidence has been presented in Paper II and again above indicating that for a large dose of radiation applied to either gamete, the pronuclei fuse definitely and without question; yet we have quoted

a fairly extensive literature indicating that they tend to remain apart under certain conditions. The matter might be dropped on the grounds that other radiations and other kinds of test material were used in the previous cases, except for the fact that G. Hertwig[5] also used a species of sea urchin (*Parenchinus miliaris*). Thus, it would perhaps be well to cite the evidence for lack of fusion of pronuclei as presented by Hertwig.

After observing that the degree of abnormality increases with exposure up to a certain point beyond which it decreases again in certain forms, Hertwig set out to discover whether cytological evidence could be obtained in sea urchin material to confirm the hypothesis that heavily treated sperm may enter the egg, stimulate it to development, but not participate in its subsequent mitotic activity. Figure 6 is a reproduction of the kind of evidence he found.

It will be seen that fusion of the pronuclei occurs rather completely, if not entirely so, even in this case. Strikingly, however, the late prophase stage displays a small body of deeply staining material lying free in the cytoplasm. Hertwig was led to believe that this is the irradiated sperm pronuclear material which in some way becomes separated from the active nucleus—indeed a reasonable expectation from the morphological characteristics displayed. With this in mind, similar stages of our material were examined for the

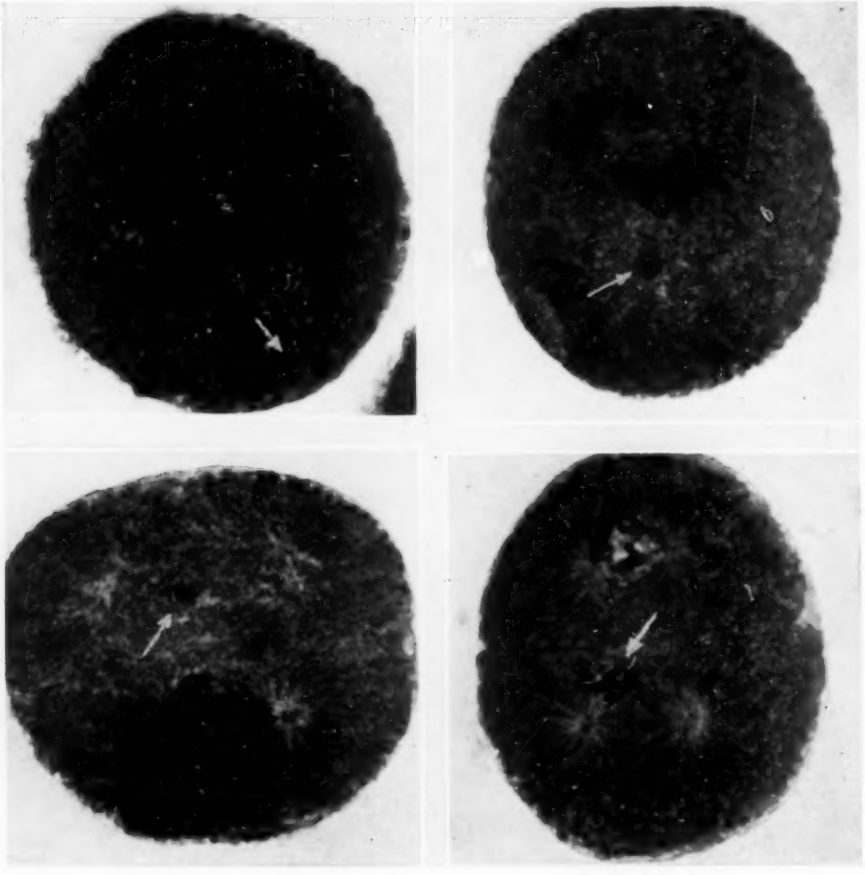

FIG. 7. Photomicrographs of *Arbacia punctulata* material displaying a body which has all the appearances of being the same as the extra-nuclear one believed by Hertwig to be irradiated sperm pronuclear material.

presence of such bodies. Figure 7 shows the kind of thing we were able to find in a good many instances. It is thus clear that our material contained bodies having appearances similar to if not precisely the same as those described by Hertwig.

Granting that this body might well be isolated sperm material, we set out to trace its previous history. Should this be isolated sperm material, as believed, it seems that evidence of its independent existence should be found all the way back to the pronuclei stages. In our case, however, the evidence of such continuity was even less than Hertwig's which indeed was scant enough. In our material, the late prophase nuclei displayed no heavily staining bodies as did Hertwig's. Almost without exception, the early prophase stages were as free of any such object as indicated by the photomicrographs in the top row of Figure 4. It seems to us, therefore, that the extra-nuclear body of the late mitotic stages must arise *de novo*. Just where it first appears is not clear, but it seems improbable that it can represent exclusively sperm pronuclear material which is aborted off by the late prophase nucleus. As concrete evidence that this body is not irradiated sperm pronuclear material, we may state that it can also be found when nonirradiated sperm are used and in the case of irradiated eggs.

Thus, after considerable apprehension, it seems that we may safely and finally conclude that for the conditions used, the pronuclei fused to the extent that the individual elements could not be distinguished. As yet our investigations have not covered cytological evidence as to whether higher doses of radiation would tend to cause the pronuclei to remain apart; but, in this connection, it is to be emphasized that the dosage used (62,400 r) was adequate to produce close to the maximum delay in cleavage and nearly 100 per cent multipolar cleavage, thus making the possibility of incomplete fusion for higher doses seem unlikely. While there is some difference between Hertwig's findings and ours, it seems to be more a matter of interpretation than observation. Hertwig's strongest evidence of incomplete fusion is based on the fact that the cleavage cells appear to have more nearly the haploid rather than the diploid number of chromosomes. Considering the confusion that may arise in connection with this kind of evidence, it seems not quite adequate to settle the question completely. In any case, the finding of the extra-nuclear bodies in the late mitotic stages of control and irradiated egg materials surely takes precedence over this evidence.

While we have indicated that as long as the irradiated sperm is able to penetrate the egg, it will fuse with the egg nucleus in case of *Arbacia punctulata*, we do not wish to imply that such may be the case generally. Packard's work with *Nereis* material and that of others with *Amphibia* material (including unpublished work of our own) are so abundantly clear, indicating that pronuclei may be caused to remain apart by irradiating gametes, there seems little doubt about it. We therefore take the position that the behavior of pronuclei of different forms may vary in this respect.

DISCUSSION

Having thus disposed of the question of the fusion of pronuclei, and with the assurance that for doses capable of producing close to 100 per cent multipolar cleavage there is fusion to the extent that the separate elements cannot be distinguished, we wish to return to the matter of multipolar cleavage and indicate what appears to be an important mechanism of cell death.

It is a recognized biological fact that the loss of chromatin usually results in serious injury to a cell and most often in cell death. Hence, shortage of chromatin in cells resulting from multipolar cleavage (or any other type of action) may be expected to be injurious or lethal. From what has been said, it appears that irradiation in certain cases may act on nuclear material in such a way as to cause accessory asters to form and that these in turn act during mitosis

to cause the chromatin ordinarily intended for two cells to be distributed among more than two, thus causing a shortage of chromatin in the cell progeny and in most cases cell death. The loss of chromatin in irradiated cells due to other means* has been extensively described in the literature, but little attention has been given to loss due to multipolar cleavage especially when accessory astral systems appear to be the inciting agents. In emphasizing this, we recognize the fact that accessory asters have been induced in cells by a variety of agents with the consequent multipolar cleavage and cell death. However, it is nonetheless significant that irradiation may cause cell death by this procedure.

Recognizing that chromatin may become abnormally distributed in cells after exposure to radiation and taking into account one of the significant theories of cancer, we are able to indicate how radiation by the same mechanism of action may act in the well known dual capacity to produce death in cells on the one hand and malignant growth on the other. Boveri, a good many years ago (see the 1929 translation), set forth what remains today as one of the most plausible theories of cancer. Basing his theory on observations of multipolar cleavage in sea urchin eggs by polyspermy, Boveri pointed out that loss of precisely the right chromosome component might be expected to unleash certain malignant behavior on the part of the daughter cells.

While, in the light of more recent genetic development, it is clear that far reaching biological changes (including cell death and perhaps malignancy) may result from modifications involving much less than whole chromosomes, the modern conception of the cancer problem attests the feasibility of the broader aspects of the Boveri Theory. In a recent U. S. Public Health Report (Reprint No. 2008) is a paper prepared by a committee of prominent investigators† appointed by the Surgeon General to "formulate, as far as could be done, the fundamental aspects of the cancer problem." In this report the following statement appears: "The new property (malignant) of the cell appears to develop suddenly, becomes a fixed character, and is transmitted to its descendants. It gives evidence of being a somatic mutation."

Thus, since cancer may possibly result from mutation, since mutation may be induced by abnormal distribution of chromatin and since cells usually die as the result of such distribution, it seems clear that radiation may by the same mechanism of action act in the dual (seemingly paradoxical) capacity to produce either death or malignant growth.

SUMMARY

1. It has been observed that application of high energy radiation to either gamete of *Arbacia punctulata* just prior to fertilization will, in addition to causing delay in the onset of cleavage, also cause the cleavage to be multipolar; in fact, close to 100 per cent of the individuals in a sample will be found to manifest this effect if the dose administered has been adequate.

2. The reaction has a definite threshold dose and goes to completion in a fairly narrow range of dosage.

3. Although several possibilities were investigated, there is no evidence that delay in cleavage and multipolar cleavage are dependent on the same change produced in the cells by the irradiation.

4. The multipolar condition is not due to polyspermy.

5. The cytokinetic and karyokinetic rhythms are not thrown out of phase with respect to each other.

6. For doses of radiation that will produce close to 100 per cent multipolar cleavage in the samples of material, there is no evidence on incomplete fusion of the pronuclei.

7. The first signs of multipolarity are the appearance of accessory asters. These ap-

* Such as fragmentation and failure of whole or parts of chromosomes to go on the equatorial plate properly during mitosis.

† Consisting of Stanhope Bayne-Jones, Ross G. Harrison, C. C. Little, John Northrop and James B. Murphy.

parently act to cause the chromatin ordinarily predestined for two cells to be divided among several, thus causing chromatin deficiencies in the cell progeny.

8. By the process of elimination, it appears that the accessory asters are formed as a result of changes produced in the nuclear material by the irradiation.

9. It is an interesting fact, although no significance has been attached to it as yet, that the multipolar condition may be induced by irradiation of half a normal nucleus—that is, a gamete.

10. On the basis of the fact that chromatin deficiency usually results in cell death, it has been pointed out that probably one of the important mechanisms by which irradiation causes cell death is the production of accessory asters, which in turn cause the chromatin to be abnormally distributed at the time of mitosis.

11. Further, in view of the fact that chromatin modification stands as one of the plausible explanations of cancer, we are able to point out how radiation may, by the same mechanism of action, function in the well known dual capacity to produce cell death on the one hand and malignancy on the other.

REFERENCES

1. Boveri, T. Ueber mehrpoligie Mitosen als mittel zur Analyse der Zellkerus. *Verhandl. d. phys.-med. Gesellsch. zu Würzb.*, 1902, *35*.
2. Boveri, T. The Origin of Malignant Tumors. Translated by Marcella Boveri. Williams & Wilkins Co., Baltimore, 1929.
3. Dalcq, A. Interprétation cytologique des effets, sur la gastrulation, de l'irradiation d'un des gamètes, chez Rana fusca. *Compt. rend. Soc. de biol.*, 1930, *104*, 1055–1058.
4. Hertwig, O. Die Radiumkrankheit tierischer Keimzellen. Ein Beitrag zur experimentellen Zeugungs- und Vererbungslehre. *Arch. f. mikr. Anat.*, 1911, *77*, 1–95; 97–164.
5. Hertwig, G. Das Schicksal des mit Radium bestrahlten Spermachromatins im Seeigelei. *Arch. f. mikr. Anat.*, 1912, *79*, 201–241.
6. Lea, D. E., Haines, R. B., and Coulson, C. A. The mechanism of bactericidal action of radioactive radiations. *Proc. Roy. Soc. Lond.*, s.B., 1936, *120*, 47–76.
7. Lorenz, K. P., and Henshaw, P. S. Action of 200 kv. x-rays on *Achromobacter fischeri*. In press.
8. Oppermann, K. Die Entwicklung von Forelleneiern nach Befruchtung mit radiumbestrahlten Samenfäden. II. Das Verhalten des Radiumchromatins während der ersten Teilungsstadien. *Arch. f. mikr. Anat.*, 1913, *83*, 307–323.
9. Packard, C. Effect of radium radiations on development of Chaetopterus. *Biol. Bull.*, 1918, *35*, 50–71.
10. Packard, C. Effect of radium radiations on fertilization of Nereis. *J. Exper. Zool.*, 1914, *16*, 85–129.
11. Simon, S. Effets de l'irradiation d'un des gamètes sur la gastrulation, chez Rana fusca. *Compt. rend. Soc. de biol.*, 1930, *104*, 1052–1055.
12. Strangeways, T. S. P., and Hopwood, F. L. Effects of x-rays upon mitotic cell division in tissue culture in vitro. *Proc. Roy. Soc. Lond.*, s.B., 1926, *100*, 283–293.
13. Sonnenblick, B. P. X-radiation of the mature gametes of Drosophila melanogaster; cytologic abnormalities and egg mortality. *Genetics*, 1938, *23*, 169.
14. U. S. Public Health Report. Fundamental Cancer Research. Vol. 53, 2121–2130. Reprint 2008.

THE AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY

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Publisher: CHARLES C THOMAS, 220 East Monroe St., Springfield, Illinois.

Issued Monthly. Subscription $10.00 per year, $11.00 in Canada and $12.00 in foreign countries. Advertising rates submitted on application: Editorial office, 110 Professional Building, Detroit, Mich. Office of publication 220 E. Monroe St., Springfield, Ill. Information of interest to all readers will be found on page iv.

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Twenty-fifth Annual Meeting: Hotel Waldorf Astoria, New York City, June 10–11, 1940.

EDITORIAL

THOMAS ALLEN GROOVER
1877–1940

THOMAS ALLEN GROOVER was born at Pidcock in southern Georgia on May 1, 1877, a son of Thomas Alfred and Sarah Jane (Joiner) Groover. His father, who was a farmer, was a Confederate soldier during the Civil War and had lost

an arm in action. Dr. Groover received his early education in the public schools of Brooks County, Georgia. Because of financial considerations it did not seem possible for him to continue his education, but through the good offices of the Hon. Hoke Smith of Georgia, who was Secretary of the Interior in President Cleveland's Cabinet, he was appointed as assistant messenger in the Department of the Interior. He then came to Washington in 1893 and resided there all the remainder of his life. In 1894 he entered the Medical Department of Columbia University, which later became The George Washington University, and graduated therefrom in 1898. In 1926 his alma mater conferred upon him the degree of Doctor of Science. After internship at the Garfield Memorial Hospital he was appointed physician with the Isthmian Canal Commission and in that capacity spent the next year in Nicaragua.

Dr. Groover returned to Washington in 1900 and entered the general practice of medicine. At the same time he began work in roentgenology at the Central Dispensary and Emergency Hospital. Although he did not completely specialize in radiology until 1912, he was actively engaged in that field from his entry into it in 1900 up to within three months of his death which occurred on April 20, 1940. It was in those early days from 1900 to about 1904 or 1905 that he suffered the injuries to his hands which resulted in amputation through the left forearm in 1926 and in final involvement of the right axilla and lung which cost him his life.

Dr. Groover was closely associated with the scientific progress and the organizational development of radiology in this country during the entire first forty years of the present century. He made numerous contributions to the literature and was always interested and quietly helpful in everything that affected the welfare of the specialty that he loved. He was insistent, however, that the radiologist is primarily a physician, and as such he always established a personal relationship with every patient who came under his care. His membership in medical organizations included the following: Medical Society of the District of Columbia, of which he was President in 1925; Fellow of the American Medical Association; Fellow of the American College of Physicians; member of the Southern Medical Association of which he was Vice-President in 1924; member of the American Roentgen Ray Society, and its President in 1925; member of the Radiological Society of North America; Fellow of the American College of Radiology in which he served both as President and as Chancellor.

Dr. Groover's work as a practicing radiologist was characterized by the utmost painstaking care and attention to detail. He not only required the best possible technical work but spared no time nor personal effort to arrive at a correct interpretation and final diagnosis. He had developed in himself to a very high degree those qualities which are indispensable in the good physician, accuracy in observation and a keen sense of relative values. He was a diagnostician of unusual ability. In manner Dr. Groover was quiet and reserved. Being of a very studious habit, he made it a rule to spend at least one hour a day in the reading of medical literature. He had great qualities both of mind and heart which were unusual and outstanding. His ability as an organizer and executive was well known. His careful, methodical attention to all the details of bookkeeping, records and management laid the foundation for his professional work. He always looked upon business arrangements, however, as a means to more important ends. He was first and last a physician. Even radiology, in every branch of which he was proficient, he insisted must always be looked upon as an integral part of general medical practice. His outstanding mental characteristics were patience and a great capacity for methodical, painstaking care in every diagnostic and therapeutic procedure. His dominant moral characteristic was a keen sense of justice, right and fair dealing. He had an unfailing patience in compromising differ-

ences of opinion among his associates, a sane judgment in arriving at important decisions, and above all, a kindly, tolerant charity toward all with whom he could not agree. He will be greatly missed by his close associates who were accustomed to call upon him almost daily for his helpful counsel, and his loss will be keenly felt in many organizations in which his advice was highly valued. His death adds another martyr to the long roll of those who have sacrificed their lives in the interests of science and humanity.

Arthur C. Christie

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

Items for this section solicited promptly after the events to which they refer.

MEETINGS OF ROENTGEN SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. C. B. Peirce, Royal Victoria Hospital, Montreal, Canada. Annual Meeting: Hotel Statler, Boston, Mass., Oct. 1–4, 1940.

AMERICAN COLLEGE OF RADIOLOGY
Secretary, Mac F. Cahal, 540 N. Michigan Ave., Chicago, Ill. Next Annual Meeting: Commodore Hotel, New York City, June 12, 1940.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. J. T. Murphy, 421 Michigan St., Toledo, Ohio. Annual meeting: New York City, June 10–14, 1940.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary, Dr. D. S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y. Annual meeting: Cleveland, Ohio, Dec. 2–6, 1940.

RADIOLOGICAL SECTION, BALTIMORE MEDICAL SOCIETY
Secretary, Dr. Walter L. Kilby, Baltimore. Meets third Tuesday each month, September to May.

RADIOLOGICAL SECTION, CONNECTICUT MEDICAL SOCIETY
Secretary, Dr. Max Climan, 242 Trumbull St., Hartford, Conn. Meets twice annually in May and September.

SECTION ON RADIOLOGY, ILLINOIS STATE MEDICAL SOCIETY
Secretary, Dr. H. W. Ackemann, 321 W. State St., Rockford, Ill. Next meeting, Peoria, Ill., May 21–23, 1940.

RADIOLOGICAL SECTION, LOS ANGELES CO. MED. SOC.
Secretary, Dr. Wilbur Bailey, 2007 Wilshire Blvd., Los Angeles, Calif. Meets on second Wednesday of each month at County Society Building.

RADIOLOGICAL SECTION, SOUTHERN MEDICAL ASSOCIATION
Secretary, Dr. Roy G. Giles, Temple, Texas.

BROOKLYN ROENTGEN RAY SOCIETY
Secretary, Dr. L. J. Taormina, 1093 Gates Ave., Brooklyn, N. Y. Meets monthly on first Tuesday, October to April.

BUFFALO RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Joseph S. Gian-Franceschi, 610 Niagara St., Buffalo, N. Y. Meets second Monday of each month except during summer months, place of meeting selected by the host.

CHICAGO ROENTGEN SOCIETY
Secretary, Dr. C. J. Challenger, 3117 Logan Blvd. Meets second Thursday of each month October to May inclusive at the Hotel Sherman.

CINCINNATI RADIOLOGICAL SOCIETY
Secretary, Dr. J. E. McCarthy, 707 Race St., Cincinnati, Ohio. Meets third Tuesday of each month, October to May, inclusive.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary, Dr. H. A. Mahrer, 10515 Carnegie Ave. Meets at 6:30 P.M. at Mid-Day Club rooms on fourth Monday each month, October to April, inclusive.

DENVER RADIOLOGICAL CLUB
Secretary, Dr. P. R. Weeks, 520 Republic Bldg., Denver, Colo. Meets third Friday of each month.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY
Secretary, Dr. E. R. Witwer, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Medical Society Building.

FLORIDA STATE RADIOLOGICAL SOCIETY
Secretary, Dr. J. N. Moore, 210 Professional Bldg., Ocala, Florida. Meetings in May and November.

GEORGIA RADIOLOGICAL SOCIETY
Secretary, Dr. R. C. Pendergrass, Prather Clinic Bldg., Americus, Ga. Meets in November and at annual meeting of Medical Association of Georgia in the spring.

ILLINOIS RADIOLOGICAL SOCIETY
Secretary, Dr. Wm. DeHollander, St. John's Hospital, Springfield, Ill. Meetings held quarterly, on the fourth Sunday of the month.

INDIANA ROENTGEN SOCIETY
Secretary, Dr. C. C. Taylor, 23 E. Ohio St., Indianapolis, Ind. Meeting held the second Sunday in May annually.

KENTUCKY RADIOLOGICAL SOCIETY
Secretary, Dr. J. C. Bell, 402 Heyburn Bldg., Louisville. Meets annually in Louisville on third Sunday afternoon in April.

LONG ISLAND RADIOLOGICAL SOCIETY
Secretary, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:30 P.M.

MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS
Secretary, Dr. J. E. Lofstrom, 1536 David Whitney Bldg., Detroit. Three meetings a year, Fall, Winter, Spring.

MILWAUKEE ROENTGEN RAY SOCIETY
Secretary, Dr. I. I. Cowan, Mt. Sinai Hospital, Milwaukee, Wis. Meets monthly on first Friday at University Club.

MINNESOTA RADIOLOGICAL SOCIETY
Secretary, Dr. J. P. Medelman, 572 Lowry Medical Arts Bldg., St. Paul.

NEBRASKA RADIOLOGICAL SOCIETY
Secretary, Dr. D. A. Dowell, Medical Arts Bldg., Omaha, Nebr. Meets third Wednesday of each month, at 6 P.M., at either Omaha or Lincoln.

NEW ENGLAND ROENTGEN RAY SOCIETY
Secretary, Dr. A. O. Hampton, Massachusetts General Hospital, Boston, Mass. Meets monthly on third Friday, Boston Medical Library.

RADIOLOGICAL SOCIETY OF NEW JERSEY
Secretary, Dr. W. J. Marquis, 198 Clinton Ave., Newark. Meets annually at time and place of State Medical Society. Mid-year meetings at place chosen by president.

NEW YORK ROENTGEN SOCIETY
Secretary, Dr. R. D. Duckworth, 170 Maple Ave., White Plains, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 8:00 P.M.

NORTH CAROLINA ROENTGEN RAY SOCIETY
Secretary, Dr. Major Fleming, Rocky Mount, N. C. Annual meeting at time and place of State Medical Society. Mid-year scientific meeting at place designated.

CENTRAL NEW YORK ROENTGEN RAY SOCIETY
Secretary, Dr. C. F. Potter, 820 S. Crouse Ave., Syracuse. Three meetings a year—January, May, November.

PACIFIC ROENTGEN CLUB
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

PENNSYLVANIA RADIOLOGICAL SOCIETY
Secretary, Dr. L. E. Wurster, 416 Pine St., Williamsport, Pa. Next annual meeting, Hershey Hotel, Hershey, Pa., May 17–18, 1940.

PHILADELPHIA ROENTGEN RAY SOCIETY
Secretary, Dr. B. R. Young, Temple University Hospital. Meeting first Thursday of each month from October to May inclusive, at 8:15 P.M., in Thompson Hall, College of Physicians, 19 S. 22d St.

PITTSBURGH ROENTGEN SOCIETY
Secretary, Dr. H. W. Jacox, 4800 Friendship Ave., Meetings held second Wednesday each month, 4:30 P.M., October to June at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y.
Secretary, Dr. S. C. Davidson, 277 Alexander St. Meets on second Thursday from October to May, inclusive, 8 P.M., Rochester Academy of Medicine Building.

ST. LOUIS SOCIETY OF RADIOLOGISTS
Secretary, Dr. W. K. Mueller, University Club Bldg. Meets fourth Wednesday of October, January, March and May, at a place designated by the president.

SAN FRANCISCO RADIOLOGICAL SOCIETY
Secretary, Dr. H. A. Hill: 450 Sutter St., San Francisco. Meets monthly on third Thursday at 7:45 P.M., first six mouths at Toland Hall, second six months at Lane Hall.

* Secretaries of Societies not here listed are requested to send the necessary information to the Editor.

South Carolina X-Ray Society
Secretary, Dr. Hillyer Rudisill, Jr., Roper Hospital, Charleston. Meets in Charleston on first Thursday in November, also at the time and place of South Carolina State Medical Association.

Tennessee Radiological Society
Secretary, Dr. F. B. Bogart, 311 Medical Arts Bldg. Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. L. W. Baird, Scott and White Hospital, Temple, Texas. Next annual meeting, January 18, 1941, Sherman, Texas.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7 p.m. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets every Thursday from 4:00–5:00 p.m., Room 301, Service Memorial Institute.

Virginia Radiological Society
Secretary, Dr. V. W. Archer, University Hospital, University, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. K. J. Holtz, American Bank Bldg., Seattle. Meets fourth Monday of each month at the College Club, Seattle.

Cuba

Sociedad Cubana de Radiologia y Fisioterapia
Secretary, Dr. Francisco Padron, Enrique, Villuendas 64, Havana, Cuba. Meets monthly in Havana.

British Empire

British Institute of Radiology Incorporated with the Röntgen Society
Meets monthly on third Thursday, from November to June inclusive, at 8:15 p.m., 32 Welbeck St., London.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets on the third Friday of each month during the winter at 8:15 p.m. at the Royal Society of Medicine, 1, Wimpole St., London, W. 1.

Faculty of Radiologists
Secretary, Dr. Barbara M. Key, 32 Welbeck St., London, W. 1, England.

Section of Radiology and Medical Electricity, Australasian Medical Congress
Secretary, Dr. H. M. Cutler, 139 Macquarie St., Sydney, New South Wales.

Radiological Section of the Victorian Branch of the British Medical Association
Secretary, Dr. Keith Hallam, St. George's Hospital, K.E.W., Melbourne, E. 4, Victoria, Australia. Meets monthly from March to November inclusive for scientific discussion.

Canadian Association of Radiologists
Secretary, Dr. A. C. Singleton, Medical Arts Bldg., Toronto, 5, Ontario.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext., Halifax, N.S.

Radiological Section, New Zealand British Medical Association
Secretary, Dr. Colin Anderson, Invercargill, New Zealand. Meets annually.

Continental Europe

Belgian Society of Roentgenology
Secretary, Dr. J. Boine, Avenue des Alliés, 134, Louvain (Belgium). Meets monthly on second Sunday at d'Egmonds Palace, Brussels, except in the summertime.

Sociedad Espanola de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7. Madrid, Spain. Meets monthly in Madrid.

Société de Radiologie Médicale de France
Meets monthly on second Tuesday, except during months of August and September, 12 Rue de Seine, Paris.

Société Suisse de Radiologie (Schweizerische Röntgen-Gesellschaft)
Secretary for French language, Dr. A. Grosjean La Chaux de Fonds.
Secretary for German language, Dr. Scheurer, Molzgasse, Biel. Meets annually in different cities.

Société Francaise d'Electrothérapie et de Radiologie Médicale
Meets monthly on fourth Tuesday, except during months of August and September, 12 Rue de Seine, Paris.

Association of German Roentgenologists and Radiologists in Czecho-Slovakia
Secretary, Dr. Walter Altschul, German University, Prague, 11.52.

Deutsche Röntgen-Gesellschaft (Gesellschaft für Röntgenkunde und Strahlenforschung)
Meets annually in April, alternating one year in Berlin, one year in some other German city. Meets in addition every two years with the Gesellschaft deutscher Naturforscher und Aerzte.
Permanent Secretary, Professor Dr. Haenisch, Klopstockstrasse 10, Hamburg, Germany.

Süd- und Westdeutsche Röntgengesellschaft
Meets annually in different cities.

Nord- und Ostdeutsche Röntgengesellschaft
Meets annually in different cities.

Dutch Society of Electrology and Roentgenology
Holds two meetings a year in Amsterdam, one in the spring, and one in the fall.

Societa Italiana Radiologia Medica
Secretary, M. Ponzio, University of Turin, Prof. Turin

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banul Mărăcine, 30, S. I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad, USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Leningrad Roentgen Ray Society
Secretaries, Drs. S. G. Simonson and G. A. Gusterin. Meets monthly, first Monday at 8 o'clock State Institute of Roentgenology and Radiology, Leningrad.

Moscow Roentgen Ray Society
Secretaries, Drs. L. L. Holst, A. W. Ssamygin and S. T. Konobejevsky. Meets monthly on first Monday at 8 o'clock.

Polish Society of Radiology
Secretary, Dr. Jan Kochanowski, 45 Gornoslazka St., Warsaw. Meets annually.

Warsaw Section, Polish Society of Radiology
Secretary, Dr. B. Krynski, 11 Zielna St. Meets once a month except in the summertime.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association. Each of the following societies, with exception of the Denmark Society, meets every second month except in the summertime:

Society of Medical Radiology in Sweden
Meets in Stockholm.

Society of Medical Radiology in Norway
Meets in Oslo.

Society of Medical Radiology in Denmark
Secretary, Dr. G. Biering, Copenhagen. Meets the second Wednesday of each month from October to July in Copenhagen, at 8 'oclock in the State Institute of Roentgenology.

Society of Medical Radiology in Finland
Meets in Helsingfors.

Vienna Roentgen Society
Meets first Wednesday of each month, at 6:30 p.m. at Zentral-Röntgen Institut des allgemeinen Krankenhauses Alserstrasse 4.

Orient

Japan X-Ray Association
c/o Orthopedic Surgery, Tokyo Imperial University. Meets annually in April.

Kinki Roentgen-Abend Society
Director, Dr. Prof. Taiga Saito, Ogawaoike Tyoto Japan. Meets bi-monthly on third Sunday.

BULLETIN OF THE INTER-SOCIETY COMMITTEE FOR RADIOLOGY

THE WASHINGTON SCENE

Although the so-called National Health Bill drafted by Senator Wagner last year failed to reach the Senate floor, reports from some sources are that it is currently being revised and will be reintroduced before the Seventy-Sixth Congress adjourns. Meanwhile, various bills intended to accomplish certain aims of the original bill have been introduced in the national Congress.

The Wagner-George Bill, S. 3230, upon which hearings have already been held, called for appropriation of $10,000,000 the first year for construction of hospitals in needy areas, title to remain in the federal government. The Mead Bill, S. 3246, proposed to authorize a federal appropriation of $300,000,000 for loans to states for hospitals, water, sewers, stream pollution control, and related projects and facilities. Of the total, $100,000,000 was to be devoted to hospital projects. Senator Mead, in his bill, defines a hospital as any institution for treating disease, including any health, diagnostic or treatment center, station or clinic.

A bill introduced by Senator Taft of Ohio on April 18 embodies certain of the recommendations contained in a memorandum left by representatives of the American Medical Association following a conference in Washington on January 10. It would provide that the federal government contribute, for a period of five years and from annual appropriations of $10,000,000, from 40 to 90 per cent of the cost of hospitals constructed with the approval of a National Advisory Hospital Council appointed by the Surgeon-General with the approval of the Federal Security Agency. Title to the hospitals would rest in the local jurisdiction.

In all these bills, equipment to be installed in the hospital is contemplated as a part of the cost of construction, it seems. In the case of the Wagner-George bill, at least, this would entail a certain amount of governmental supervision in the use of this equipment. The status of radiologists operating in such hospitals is a matter for conjecture.

A revised version of the Wagner-George Bill was reported out for the Senate Committee on Education and Labor, by Senator James E. Murray of Montana on April 30. The Committee frankly states in its report that the new bill is designed to accomplish part of the original Wagner Health Bill and that it is only the initial step in the Committee's projected program.

The revised bill would appropriate $10,000,000 the first fiscal year to be used for hospital construction and an equal amount for each of the five succeeding years to be used for grants-in-aid to states and subdivisions thereof for construction and maintenance of hospitals. It also authorizes the use of 2 per cent of the appropriations for the training of personnel necessary for such hospitals. Title can be acquired by the local county or state. The proposal expressly states that the hospitals are to be used for "diagnosis."

Kansas' Senator Capper is less modest in the proposals contained in his bill. Introduced on March 25, it is the revised Epstein Bill and calls for $50,000,000 the first year and indeterminate amounts in succeeding years to induce states to establish systems of compulsory health insurance under the Social Security Act.

Senator Henry Cabot Lodge of Massachusetts introduced on March 19 a bill to provide for a federal health insurance program and the furnishing of "those medical services and facilities which have become standardized in their nature, but which because of high cost are not used in many cases where their use would be unquestionably desirable."

In discussing his bill, Senator Lodge said, "I believe it is not disputed that countless instances occur every day in which x-ray examinations are desirable—nay, essential—but are not given because of the prohibi-

tive cost. The suffering which could be prevented by prompt x-ray examination is indescribable. Needless to say, the prevention of disease automatically tends to reduce the cost of caring for the disease once it has been allowed to take hold. The use of respirators and x-rays involves a technique which has become relatively standardized. In the case of the x-ray, it is not inconceivable that it would become a routine part of every physical examination were it not for the cost. In the case of people of moderate means the cost prohibits its use. In the case of persons who can afford it, the use of x-ray is known to be so unusual that its prescription sometimes causes alarm."

A fellow Bostonian, Dr. Hugh Cabot, adds fuel to the flame by continuing his self-appointed rôle of propagandist for medical reform.

Dr. Cabot, it will be recalled, is the author of an article in the April *American Magazine*, in which he airs some of his own past practices and concludes that the best way to prohibit the repetition of such ulterior practices as he confesses is to socialize medicine. He is apparently unaware of the national examining boards like the American Board of Radiology, for he leaves the impression that any doctor may set himself up as a specialist without any special qualifications. He omits any mention of the fact that strenuous efforts are being made by organized medicine, without the need for governmental regimentation, to police its own members and raise the standards for specialty practice.

Says the *Journal of the Indiana Medical Association*, commenting editorially, "Doctor Cabot forgets that only a very small per cent of M.D.'s are surgeons. Most of the conditions for which patients seek relief are medical and functional—not surgical, and one of the first duties of a doctor is to relieve the patient of worry through personal contact. Doctor Cabot is not accustomed to this phase of medical practice—he is used to going to the operating room where the patient is completely ready for the surgery that he performs. He is not called upon to see the patient through the minor difficulties for which the physician collects one and two dollar fees. The big fees of the surgical specialist are best known to him and he has had little opportunity to know about the kind of medical practice that the average physician does—not the extremist or the ultra-conservative, but just the average physician."

Mac F. Cahal
Executive Secretary

PITTSBURGH ROENTGEN SOCIETY

On Monday, April 29, 1940, the members of the Cleveland Radiological Society were the guests of the Pittsburgh Roentgen Society at a meeting and dinner at the Hotel William Penn in Pittsburgh. Fifty-six members and guests attend[illegible] and an excellent scientific program as presented. Dr. Lloyd R. Craver of the Memorial Hospital, New York City, spoke on the subject of "Bronchiogenic Carcinoma," Drs. Charles Higley and Harry Hauser of the Cleveland City Hospital spoke on the "Diagnosis and Treatment of Intrathoracic Hodgkin's Disease," and Dr. Paul G. Bovard of Tarentum, Pennsylvania, gave a paper on "Diagnostic Problems Associated with Silicosis."

DEPARTMENT OF TECHNIQUE

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A SIMPLIFIED GEIGER-MÜLLER COUNTER TUBE CIRCUIT

By VAN A. ODLE, M.D.*
WASHINGTON, D.C.

SINCE the development of the Geiger-Müller type tube in 1928[1] for the detection of minute quantities of ionizing radiant energy, there have been many improvements in both the tube and associated circuits. Numerous authors have described

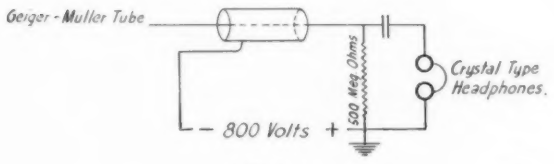

FIG. 1.

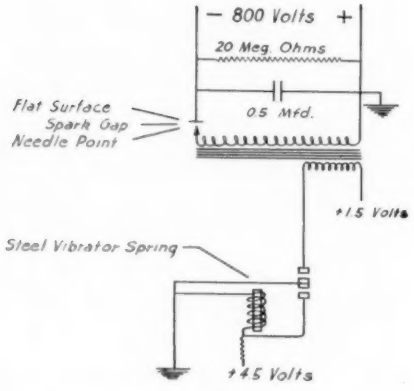

FIG. 2.

circuits for the use of this tube (Locher and Weatherwax;[2] Braestrup, Murphy and Whitaker;[3] Taft,[4] and others).

The circuit described here (Fig. 1) is more simple, compact and portable than any previously described. The successful operation of this circuit depends upon the fact that crystal type headphones are used. The high impedance of this type of headphone enables it to be connected in series with the high impedance of the Geiger-Müller tube, and a very satisfactory response is obtained without additional amplification. It is obvious that the circuit is designed for use with headphones only. In many applications of the Geiger-Müller tube this is all that is desired as in the finding of lost radium, etc.

It is desirable to have a portable power supply for use with the above described circuit. There are small portable batteries designed especially for use in stratosphere balloons. These batteries would probably be an ideal high voltage source but have not been commonly used due to their cost. A portable high voltage power supply has been described by Taft,[4] which operates upon the same principle as the power supply of an automobile radio receiver. He uses an induction coil and vacuum tube rectifier.

The power supply used by me (Fig. 2) operates upon the same principle as the one noted above but has been modified in several respects in regard to design. A separate interrupter and transformer are used. This produces greater stability in the high voltage circuit. Due to the wave form of the voltage in the secondary, a spark gap may be used as a rectifier and has been very efficient in this case, thus eliminating the necessity of using any vacuum tubes. One side of this spark gap should be a needle point and the other side a flat surface as shown in the diagram. The detector

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circuit must be shielded from the power supply circuit. In the circuits as described above there is no audible power supply noise produced in the headphones. The ground symbol as used in the diagrams refers to the metal cabinet as being at ground potential with respect to the remainder of the circuit.

The main features of this instrument are that it is very compact, simple and readily portable. The entire apparatus, with the exception of the headphones, is contained in a metal cabinet $6 \times 6 \times 6$ inches.

REFERENCES

1. Geiger, H., and Müller, W. *Phys. Ztschr.*, 1928, *29*, 839.
2. Locher, G. L., and Weatherwax, J. L. Use of Geiger-Müller counters for locating radium and for measuring gamma-ray intensities. *Radiology*, 1936, *27*, 149–157.
3. Braestrup, C. B., Murphy, E. J., and Whitaker, M. D. Radiological applications of the Geiger-Müller counter. Am. J. Roentgenol. & Rad. Therapy, 1937, *38*, 915–922.
4. Taft, R. B., Battery operated Geiger-Müller counters with a new type of voltage supply. *Radiology*, 1936, *27*, 616–617.

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